CARDIAC TROPONIN I – EARLY PREDICTOR OF HYPOXIC MYOCARDIAL INJURY AND NEONATAL OUTCOME IN PERINATAL ASPHYXIA

Dissertation Submitted

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF (BRANCH VII) M.D., (PAEDIATRIC MEDICINE)

OF

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CHENNAI – 600032

DEPARTMENT OF PAEDIATRIC MEDICINE

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI -11

MAY -2019

BONAFIDE CERTIFICATE

Certified that this dissertation entitled **"CARDIAC TROPONIN I – EARLY PREDICTOR OF HYPOXIC MYOCARDIAL INJURY AND NEONATAL OUTCOME IN PERINATAL ASPHYXIA "**is a bonafide work done by **Dr.N.KIRUTHIKA M.D.** post graduate student of Paediatric Medicine ,Tirunelveli Medical College Hospital, Tirunelveli 2016 – 2019.

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DECLARATION

I Solemnly declare that this dissertation **"CARDIAC TROPONIN I – EARLY PREDICTOR OF HYPOXIC MYOCARDIAL INJURY AND NEONATAL OUTCOME IN PERINATAL ASPHYXIA"**is the bonafide work done by me during my post graduate course in MD Paediatric Medicine (2016-2019),at the Department of Paediatrics, Tirunelveli Medical College, Tirunelveli, under the guidance and supervision of **Prof.Dr.T.R.R.Ananthy Shri,M.D.,** Professor , Department of Paediatrics, Tirunelveli Medical College,Tirunelveli-627011.This dissertation submitted to **The Tamil Nadu Dr. M.G.R.Medical University, Chennai** in partial fulfilment of the University regulations for the award of **M.D Degree in PAEDIATRIC MEDICINE** examinations to be held in May 2019.

Place : Tirunelveli **DR.N.KIRUTHIKA**

Date : May 2019

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PROTOCOL TITLE: CARDIAC TROPONIN I – EARLY PREDICTOR OF HYPOXIC MYOCARDIAL INJURY & NEONATAL OUTCOME IN PERINATAL ASPHYXIA
PRINCIPAL INVESTIGATOR: DR.N.KIRUTHIKA, MBBS.,
DESIGNATION OF PRINCIPAL INVESTIGATOR: POST GRADUATE STUDENT
DEPARTMENT & INSTITUTION: TIRUNELVELI MEDICAL COLLEGE, TIRUNELVELI

Dear Dr.N.KIRUTHIKA, MBBS., The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during The IEC meeting Held on 10.03.2017.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☐
2.	Study Protocol	☐
3.	Department Research Committee Approval	☐
4.	Patient Information Document and Consent Form in English and Vernacular Language	☐
5.	Investigator's Brochure	☐
6.	Proposed Methods for Patient Accrual Proposed	☐
7.	Curriculum Vitae of The Principal Investigator	☐
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☐
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☐
14.	Clinical Trials Registry-India (CTRI) Registration	☐

THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of The validity
4. An annual status report should be submitted.
5. The TIREC will monitor The study
6. At The time of PI's retirement/leaving the institute, The study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in The original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and The revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, The same should be documented.
   d. If there are any amendments in The trial design, These must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of The IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in The protocol must be informed.

STANDS APPROVED UNDER SEAL

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CERTIFICATE – II

This is to certify that this dissertation work title "**CARDIAC TROPONIN I – EARLY PREDICTOR OF HYPOXIC MYOCARDIAL INJURY AND NEONATAL OUTCOME IN PERINATAL ASPHYXIA"** of the candidate **DR.N. KIRUTHIKA** with registration Number **201617352** for the award of M.D. in the branch of Paediatric Medicine. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **4 percentage** of plagiarism in the dissertation.

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Sources included in the report:

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Instances where selected sources appear:

13

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CONTENTS

ABBREVIATIONS

ATP	Adenosine triphosphate
AKI	Acute kidney injury
aEEG	Amplitude integrated Electroencephalogram
β2M	Beta -2 Microglobulin
cTnI	Cardiac Troponin I
Ca^{2+}	Calcium
CBF	Cerebral blood flow
CP	Cerebral palsy
DWI	Diffusion Weighted imaging
EEG	Electroencephalogram
ECG	Electrocardiogram
ECHO	Echocardiogram
FENa	Fractional Excretion of sodium
GFR	Glomerular Filtration Rate
HIE	Hypoxic Ischemic encephalopathy
IUGR	Intra Uterine Growth Restriction
MAS	Meconium Aspiration Syndrome
MRS	Magnetic Resonance Spectroscopy
NMDA	N- Methyl D aspartate receptors
NO	Nitric oxide

NOS	Nitric oxide synthase
PIH	Pregnancy Induced Hypertension
PROM	Premature Rupture of Membranes
PPHN	Persistent pulmonary hypertension
PVL	Periventricular leukomalacia
RFT	Renal Function Test
RFI	Renal Failure Index
SVR	Systemic Vascular Resistance
SIADH	Syndrome of inappropriate antidiuretic Harmone
SNCU	Sick New Born Care Unit
UTI	Urinary Tract Infection

PROFORMA

PROFORMA FOR CARDIAC TROPONIN I – EARLY PREDICTOR OF HYPOXIC MYOCARDIAL INJURY AND NEONATAL OUTCOME IN PERINATAL ASPHYXIA

SR No :

Name : IP No:

Address: Sex: Male / Female :

Gestational Age :

Birth Weight :

Date of Birth :

Date of Discharge / Death :

Ante Natal Data :

1. Gravida :
2. An risk factors :

Maternal Delivery Data

1. Mode of Delivery : Vaginal

   Assisted

   Caesarean

Resuscitation details :

1Minute Apgar :

5minute Apgar :

10 Minute Apgar :

Need for PPV > 1minute :

Spontaneous respiration established : Yes / No

When :

Clinical Examination:

Sensorium :

Tone :

Seizure activity :

Shock :

MAP :

Duration of inotropic support :

Ventilator Support :

Tendon reflexes :

Posture :

Moro reflex :

Autonomic instability :

Pupil :

HR :

GI Motility :

Temperature :

Lab investigations :

Renal parameters :

Troponin I :

Electro cardiogram :

Echo cardiogram :

Cranial Ultrasound :

INFORMED CONSENT FORM

Study Title _____

Study Number _____

Subject's Full Name _____

Date of Birth/Age _____

Address _____

1. I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions.

   OR I have been explained the nature of the study by the Investigator and had the opportunity to ask questions

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that the sponsor of the clinical trial/project, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. However, I understand that my Identity will not be revealed in any information released to third parties or published.

4. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

5. I agree to take part in the above study

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative: _____

Signatory's Name _____ Date _____

Signature of the Investigator _____ Date _____

Study Investigator's Name _____

Signature of the Witness _____ Date _____

Name of the Witness

INTRODUCTION

Birth asphyxia accounts for major cause of morbidity and mortality in Neonates. It is estimated that of the 136 million annual births, about (10 million)5%-10% respond to simple stimulation to initiate breathing effort,3% to 6% require basic resuscitation with bag and mask (6 million), and only less than 1% (<1 million) require advanced resuscitation (0.1% chest compression and 0.05% require drugs)[1].

Central nervous system involvement occurred in 62% of infants. Indeed, in 16% of infants, involvement of only the nervous system was apparent. Central nervous system involvement without overt dysfunction of systemic organs is particularly likely after severe, acute, terminal intrapartum insults with resulting injury primarily to deep nuclear structures. Systemic organ involvement, without neurological disease, occurred in only 16% of infants. The order of frequency of systemic organ involvement in all birth asphyxia overall has been hepatic > pulmonary > renal > cardiac. In an autopsy series, cardiac involvement was the most common among involvement of systemic organs[2].With careful electrocardiographic and enzymatic studies of living infants after perinatal asphyxia, evidence of myocardial ischemia has been commonly observed.

Perinatal asphyxia leading to Hypoxic ischemic encephalopathy is a common problem causing multi organ dysfunction including myocardial

involvement which can affect the outcome. Sometimes cardiac dysfunction may be so severe that it can cause congestive cardiac failure and shock that leads to death in newborns. ECG and serum levels of cardiac enzymes can be used to demonstrate impaired myocardial dysfunction[3].

Cardiac troponin I (cTnI) was measured as an indicator of cardiac injury for a long time, but it has been of recent interest for the prediction of poor neonatal outcome in perinatal asphyxia. As ECG and ECHO could not predict the early myocardial injury, CARDIAC TROPONIN I would be a better and early marker of myocardial dysfunction in perinatal asphyxia, since it would be released within 4-6 hours of myocardial injury[4].

By diagnosing myocardial dysfunction early through Troponin I, we could recognise myocardial dysfunction early and manage accordingly with timely inotropic support. Also we could assess the severity of HIE by correlating it with troponin I levels.

STUDY JUSTIFICATION

Perinatal asphyxia is one of the leading causes of neonatal mortality and it is the most common and important cause of preventable cerebral injury occurring in the neonatal period. Perinatal asphyxia leading to HIE, also causes multiorgan dysfunction including cardiac - transient myocardial ischemia. sometimes it is so severe to cause congestive cardiac failure & shock that leads to death in newborns.

Cardiac Troponin I is a protein released from myocytes when irreversible myocardial damage occurs. Troponin I is one of the preferred markers of early myocardial injury as they have high sensitivity and specificity for the diagnosis of myocardial injury, which also correlates with the severity of HYPOXIC ISCHEMIC ENCEPHALOPATHY

Various studies were done previously measuring the troponin I levels and its correlation with HIE. The present study was done to identify cardiac Troponin I levels in HIE earlier within 6 hours of life, to anticipate and predict shock earlier and to start with timely inotropic support , thereby reducing the morbidity and mortality in HIE.

AIMS AND OBJECTIVES

1. To study the role of cardiac Troponin I in early prediction of ischemic myocardial injury in asphyxiated term neonates.
2. To correlate the cardiac Troponin, I levels with clinical severity of HYPOXIC ISCHEMIC ENCEPHALOPATHY as per SARNAT and SARNAT staging.

REVIEW OF LITERATURE

PERINATAL ASPHYXIA

Definition

Perinatal asphyxia refers to the Condition during the first and second stage of labour in which impaired gas exchange leads to fetal acidosis, hypoxemia, and hypercarbia.

CLINICAL DIAGNOSIS

1) evidence of cardio-respiratory dysfunction

2) neurological depression, defined as

- an APGAR score < 7 at 5 minutes

- arterial blood pH of < 7 or base excess greater than 16mmol/L. [5]

PATHOPHYSIOLOGY

Healthy fetus, shows adaptive responses to hypoxia- redistribution of cardiac output to the vital organs including brain, increases myocardial contractility, accelerates anaerobic glycolysis etc. Cerebral auto-regulation of cerebral blood flow initially maintains brain perfusion within a range of range 60–100 mm of Hg. With prolonged asphyxia, the early compensatory adjustments fail and Cerebral Blood Flow may become

dependent on systemic blood pressure (pressure - passive) leading to Brain hypoxia & intracellular energy failure. However, prolonged hypoxic-ischemic damage can cause neuronal death. The majority of injury leading to neuronal death occurs after recovery from the initial insult .

PRIMARY NEURONAL INJURY

Neuronal cell membranes get affected due to hypoxic-ischemic injury causing intracellular energy depletion, which leads to failure of ionic pump mechanism at the cell membrane level which leads to excess sodium, calcium and water entering the cell causing cytotoxic neuronal injury and death.

SECONDARY NEURONAL INJURY

Reperfusion of the affected neuronal tissues after a hypoxic-ischemic insult initiates a host of biochemical reactions at the cellular level.

Free Radical Injury

Reactive oxygen metabolites including oxygen and hydroxyl free radicals damage the arteriolar endothelium which stimulates xanthine oxidase production leading to generation of oxygen free radicals which overwhelm endogenous scavenger mechanisms, damage cellular lipids, proteins and nucleic acids and thereby the blood brain barrier.

Excitotoxic Amino Acid Injury

Hypoxic-ischemic insult causes release of excessive amounts of glutamate which acts on the NMDA receptors (N methyl D aspartate receptors) which thereby allows sodium and calcium to enter the neuronal cells causing immediate neuronal death from the osmolar load. The basal ganglia and perirolandic cortex - particularly sensitive to hypoxic injury in neonates. Further, these excitotoxins, because of provoking excessive calcium influx causes delayed neuronal death by activation of undesirable enzymes and secondary messenger systems (e.g. Ca2+ dependent lipases and proteases).

Nitric Oxide

Nitric oxide is generated in the cell as a result of stimulation of Nitric Oxide Synthase [NOS]. This generates another reactive metabolite peroxynitrite, causing lipid peroxidation of intracellular membranes with consequent loss of cell function.

Apoptosis

Apoptosis is regulated by genetic factors with little loss of cellular membrane integrity leading to contraction of the cells, which are subsequently consumed by macrophages. Other triggers of apoptosis

include cytokines (Tumour necrosis factor alpha), reactive oxygen metabolites and NO[5].

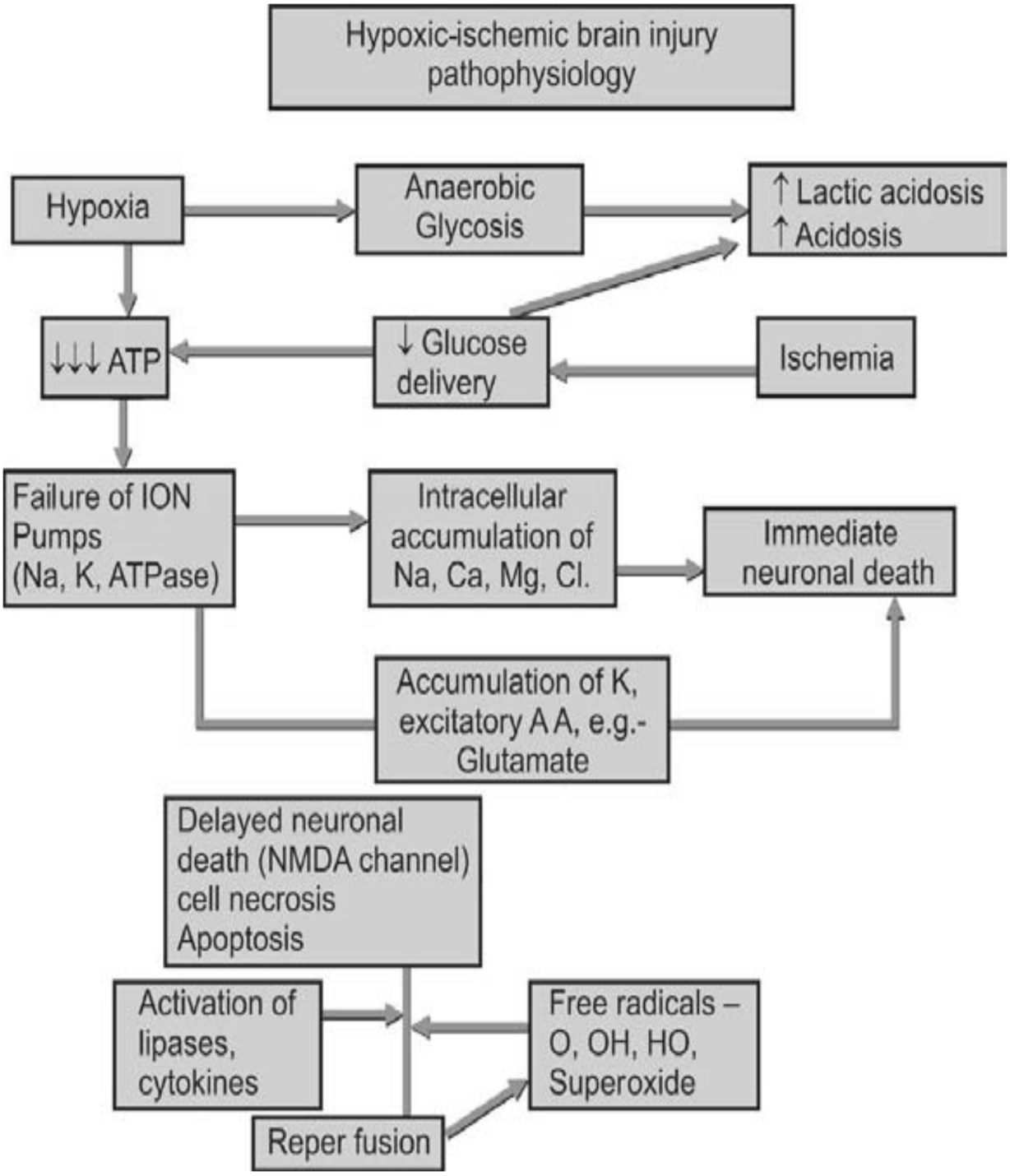


Figure 1

HYPOXIC ISCHEMIC BRAIN INJURY-PATHOPHYSIOLOGY

Adaptive responses of the fetus or newborn to asphyxia.

In response to asphyxia, the mature fetus redistributes blood flow to vital organs - heart, brain and adrenals.

1. Impairment of cerebrovascular autoregulation. Results from direct cellular injury and cellular necrosis from prolonged acidosis and hypercarbia.

2. Majority of neuronal disintegration. Occurs after termination of the asphyxia insult because of persistence of abnormal energy metabolism and low adenosine triphosphate (ATP) levels (primary energy failure).

3. Major circulatory changes during asphyxia (reperfusion phase):

a. Loss of cerebrovascular autoregulation- cerebral blood flow (CBF) becomes “pressure passive,” leading to cerebral ischemia with systemic hypotension and cerebral hemorrhage with systemic hypertension.

b. Increase in cerebral blood flow (occurs in phase of secondary energy failure) because of redistribution of cardiac output, initial systemic hypertension, loss of cerebrovascular autoregulation, and local accumulation of vasodilator factors (H+, K+, adenosine and prostaglandins).

c. In prolonged asphyxia, there is a decrease in cardiac output, hypotension and a corresponding fall in CBF.

d. The postasphyxia newborn is in a persistent state of vasoparalysis and cerebral hyperemia. Cerebrovascular hemorrhage may occur on reperfusion of the ischemic areas of the brain. In case of prolonged and severe asphyxia local tissue recirculation may not be restored due to collapsed capillaries (severe cytotoxic edema)[6].

ETIOLOGY

The most common maternal risk factors for newborns requiring resuscitation was PIH followed by oligohydramnios, multiple gestation, PROM, diabetes mellitus and UTI. IUGR was the most common fetal risk factor followed by fetal distress, prematurity, MAS and malpresentations[7].

Factors that increase the risk of perinatal asphyxia :

1. Impairment of maternal oxygenation

2. Decreased blood flow from mother to placenta

3. Decreased blood flow from placenta to fetus

4. Impaired gas exchange across the placenta or at the fetal tissue level

5. Increased fetal O2 requirement

Etiology

1. Maternal factors:

Hypertension (acute or chronic), hypotension, infection (including chorioamnionitis), hypoxia from pulmonary or cardiac disorders, diabetes, maternal vascular disease and in utero exposure to cocaine.

Lack of antenatal care, poor nutritional status, antepartum hemorrhage and maternal toxaemia were associated with higher incidence of asphyxia[8]

2. Placental factors:

Abnormal placentation, abruption, infarction, fibrosis, or hydrops

3. Uterine rupture

4.Umbilical cord accidents: prolapse, entanglement, true knot, compression

5. Abnormalities of umbilical vessels

6. Fetal factors: anemia (e.g., from fetal-maternal hemorrhage), infection, cardiomyopathy, hydrops, severe cardiac/circulatory insufficiency

7. Neonatal factors: cyanotic congenital heart disease, persistent pulmonary hypertension of the newborn (PPHN), cardiomyopathy, other forms of neonatal cardiogenic and / or septic shock, meconium aspiration syndrome, neonatal pneumonia, pneumothorax[8].

CAUSES OF ACUTE HYPOXIA

Acute intrapartum hypoxia:

- prolapsed umbilical cord
- placenta previa , placental abruption

• Sudden onset of bradycardia during labour - often idiopathic[10]

DEFINITIONS

Perinatal hypoxia, ischemia, and asphyxia. decreased oxygen (O2), blood flow, and gas exchange to the fetus or newborn respectively.

B. Perinatal / neonatal depression is a clinical term that describes the condition of the infant on physical examination in the first hour after birth. The clinical features include depressed mental status, muscle hypotonia, and / or disturbances in spontaneous respiration and cardiovascular function.

C. Neonatal encephalopathy is a clinical term that (after the first one hour of life) describes an abnormal neurobehavioral state consisting of an altered level of consciousness (including hyperalert state) with other signs of brainstem and / or motor dysfunction. It may be caused by such reversible conditions as maternal medications or hypoglycemia.

D. Hypoxic-ischemic encephalopathy (HIE) is a term that describes clinical evidence of encephalopathy & objective data to support a hypoxic-ischemic (HI) mechanism as the underlying cause for the encephalopathy.

E. Hypoxic-ischemic (HI) brain injury refers to neuropathology due to hypoxia and or ischemia as evidenced by neuroimaging or post-mortem abnormalities[11.]

In order for an acute intrapartum hypoxic event as cause of cerebral palsy (CP), the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) define 4 essential criteria .

1. Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH <7 and base deficit ≥12 mmol/L).

2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation.

3. CP of the spastic quadriplegic or dyskinetic type.

4. Exclusion of other identifiable etiologies such as trauma, coagulation disorders, infectious conditions or genetic disorders.

D. Criteria that suggest an acute intrapartum hypoxic event

1. A sentinel hypoxic event occurring immediately before or during labour

2. A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal

3. Apgar scores of 0–3 beyond 5 minutes

4. Onset of multisystem involvement within 72 hours of birth

5. Early imaging showing evidence of acute non focal cerebral abnormality[12]

CLINICAL PRESENTATION

Perinatal asphyxia can result in

CNS injury alone - 16%

CNS and other end-organ damage - 46%,

isolated non-CNS organ injury - 16%

or no end-organ damage - 22%

Clinical Features of Severe Hypoxic-Ischemic Encephalopathy: 12 to 24 Hours

Variable change in level of alertness

More seizures

Apneic spells

Jitteriness

Weakness- involving

-Proximal limbs: upper > lower (full term)

-Hemiparesis (full term)

-Lower limbs (premature)

Clinical Features of Severe Hypoxic-Ischemic Encephalopathy: 24 to 72 Hours

Stupor or coma

Respiratory arrest

Brain stem oculomotor and pupillary disturbances

Catastrophic deterioration with severe intraventricular hemorrhage

and periventricular hemorrhagic infarction (premature)

Clinical Features of Severe Hypoxic-Ischemic Encephalopathy: After 72 Hours

Persistent, yet diminishing stupor

Disturbed sucking, swallowing, gag, and tongue movements

Hypotonia > hypertonia

Weakness of

-Proximal limbs: upper > lower (full term)

-Hemiparesis (full term)

-Lower limbs or hemiparesis (premature) [13.]

MULTIORGAN SYSTEMIC EFFECTS OF ASPHYXIA

CNS

HIE, infarction, intracranial hemorrhage, seizures,

cerebral edema, hypotonia, hypertonia

CARDIOVASCULAR

Myocardial ischemia, poor contractility, tricuspid insufficiency, hypotension.

PULMONARY

Pulmonary hypertension, pulmonary hemorrhage , RDS.

RENAL

Acute tubular or cortical necrosis

ADRENAL

Adrenal hemorrhage

GIT

Gastrointestinal Perforation, ulceration with hemorrhage, necrosis

METABOLIC

Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria and Subcutaneous fat necrosis

Hematology

Disseminated intravascular coagulation.

INTRA-PARTUM FETAL MONITORING

• Electronic fetal monitoring (EFM) and fetal scalp pH monitoring:

A Fetal scalp pH of less than 7.20 indicates that delivery should be carried out rapidly. The only benefit however, in neonatal outcome seen after electronic fetal monitoring was a reduction in the incidence of early neonatal seizures.

• Fetal ECG analysis: It appears that a normal heart rate pattern may be reassuring , but an abnormal fetal heart rate pattern is poorly predictive of

fetal compromise. Close CTG monitoring with additional ECG ST-waveform correlates significantly with lower rate of acidotic umbilical artery pH compared with standard CTG monitoring .

• Fetal pulse oximetry

Near-infrared Spectroscopy: During labour, an optical probe is kept on to the fetal head via cervix to assess the anterior cerebral artery flows and oxygen saturation. Good correlation between the mean cerebral oxygen saturation shortly before delivery and the umbilical arterial acid-base status immediately after birth[14].

NEUROPATHOLOGIC FEATURES OF PERINATAL BRAIN INJURIES

- parasagittal brain injury
- periventricular leukomalacia
- selective neuronal necrosis
- focal or multifocal ischemic lesions

Parasagittal Brain Injury -Occurs in term neonates. It is classically bilateral, symmetric, and affects the parasagittal portions of the cerebral convexities (“watershed” areas between the territories of the anterior, middle, and posterior cerebral arteries) results in prolonged partial asphyxia. This type of injury affects the motor cortex - the portion

responsible for proximal extremity function results in seizures, hypotension or both. The upper extremities are often more severely affected. These patients present with spastic quadriplegia and seizure disorders later in life.

Periventricular Leukomalacia

PVL is the most common injury in preterm babies. Before 32 weeks of gestation, blood vessels penetrate the cortex from the pial surface. Fetuses of this age have short penetrators (which end in the subcortical white matter) and long penetrators (which extend deeper into the brain). This results in relatively poor vascularization of the periventricular white matter, which predisposes premature infants to ischemic injury. The areas that are most prone to damage are the centrum semiovale and the optic (trigone and occipital horns) and acoustic (temporal horn) radiations. Because of involvement of the lower extremity axons of the corticospinal tract, which are periventricular in location, these patients present later with spastic diplegia. Visual field disorders are also characteristic of PVL because of damage that occurs within the optic radiations.

Selective Neuronal Necrosis

Selective Neuronal Necrosis is the most common pattern. The sequelae include mental retardation, spastic quadriparesis and seizures.

Choreoathetosis and dystonia occur if the thalamus and basal ganglia are involved. Bulbar and pseudobulbar palsy occur if the brainstem and tegmentum are affected. Pathogenesis include Hypoperfusion with subsequent reperfusion injury and glutamate-induced injury.

Diffuse neuronal injury

Occurs after severe, very prolonged hypoxic–ischemic insults in both term and premature infants. It affects the cortex, hippocampus, cerebellum, and anterior horn cells of the spinal cord. Within the cortex, the injury is more marked in the depth of the sulci than in the gyri. With more severe injuries, the more differentiated visual (calcarine) cortex and the perirolandic cortex may be damaged[15].

POSTNATAL INVESTIGATIONS

Cranial Ultrasound

A high proportion of encephalopathic infants had evidence of major recent and evolving brain injury on early CUS imaging, suggesting prolonged or severe acute exposure to hypoxia-ischemia (HI). Early abnormalities were a significant predictor of death[16].cerebral edema recognized by a generalized increase in echo-density, a loss of anatomical landmarks, indistinct sulci and compression of the ventricles.

'Slit –like' ventricles are seen normally in the first 24 hours in term infants, and are only abnormal if persisting for more than 36 hours. Later ultrasound scan findings associated with a poor neurodevelopmental outcome include bilateral, uniformly echogenic injury, diffuse parenchymal echodensities (which represent neuronal necrosis); multi-focal cystic changes; periventricular echodensities; and ventriculomegaly with cortical atrophy.

CT Scan

CT scan-prognostic factor when done about 4-6 weeks after asphyxia. In acute stages, CT shows reversal sign - diffuse cerebral hypodensity with loss of gray white differentiation but with relatively increased density of deep nuclear structures. In chronic cases CT shows changes in basal ganglia and thalamus. These areas express a featureless appearance, with loss of distinction of deep nuclear structures and usually clearly decreased attenuation of these structures, which gradually deteriorates over several months. Rarely the injury can develop calcification. Because of the relatively superficial nature of the parasagittal cerebral injury it is more difficult to appreciate it on CT scan unless it is very severe. Periventricular leukomalacia in preterm infants can be seen in CT scans as periventricular hypodensity with a propensity for involvement of anterior and posterior periventricular areas.

Magnetic Resonance Imaging (MRI)

MRI is the most sensitive and specific imaging modality for evaluating suspected neonatal HIE. Conventional MRI is less sensitive than newer imaging techniques like DWI and MRS in diagnosing acute brain injury; however, they can help to exclude other causes of encephalopathy such as congenital malformation, neoplasm, cerebral infarction and hemorrhage[17].

DWI often can show abnormalities within the first few hours after the insult and is pragmatically useful. DWI reveals restricted water diffusion not apparent on conventional MRI by detecting differences in rates of diffusion of water protons. Atrophy of thalamus, basal ganglia usually accompanied by increased signal on T2W images is prominent especially in children with extra-pyramidal involvement. The sequelae of PVL are distinct and consists of decreased periventricular white matter, especially in the peri-trigonal area, compensatory ventricular dilation and increased signals in periventricular white matter on T2W images. MRI is useful in establishing the clinical diagnosis, assessing the severity of injury and thereby prognosticating the outcome[18].

Cerebral Blood Flow Velocities

Using pulsed wave duplex Doppler with real-time analysis of the Doppler signal from a major cerebral artery (often the anterior), the

cerebral blood flow can be determined. The end tidal CO2 should be kept in the normal range because hypercapnia causes cerebral acidosis and may cause cerebral vasodilation which may cause more flow to uninjured areas with relative ischemia to damaged areas and extension of infarct size. Excessive hypocapnia may decrease CBF. Hyperventilation is not recommended. The decreasing diastolic blood flow velocity in relation to the peak systolic blood flow velocity (Pourcelot's resistivity index <0.55) is associated with a poor outcome in asphyxiated infants. The cerebral blood flow velocities can take 24 hours to become abnormal following hypoxia-ischemia, and have been found to be of little prognostic value if performed at 6 hours.

Magnetic Resonance Spectroscopy

Calculation of absolute metabolite concentrations and relaxation times measured within the first 4 days after birth would improve prognostic accuracy and enhance the understanding of underlying neurochemical changes in neonates with neonatal encephalopathy[19].

Intra-cerebral energy states can be measured in vivo by magnetic resonance spectroscopy (MRS) technique. Phosphocreatinine (PCr) and inorganic phosphate (Pi) can be measured from the phosphorus-31 spectra. The PCr/Pi ratio represents the phosphorylated energy status within the brain, and a low PCr/Pi ratio in asphyxiated neonates is associated with

later neurodevelopmental impairment. Prolonged high levels of lactate peaks predict a bad outcome.

EEG and Amplitude Integrated EEG (aEEG)

Cerebral Function Monitoring

The severity of EEG abnormalities and their duration are of prognostic importance. Recovery of normal EEG background by day 7 is associated with a normal outcome. In contrast a burst suppression pattern or isoelectric pattern on any day is invariably associated with a poor outcome. Amplitude-integrated EEG recordings (Cerebral function monitor) obtained continuously from bipolar electrodes have recently been advocated as an objective tool for early prediction of poor outcome.

Use of aEEG monitoring can predict outcome, with a high degree of accuracy, after birth asphyxia, within the first six hours after birth. The predictive value of a suppression-burst pattern was, however, somewhat lower than the other background patterns. The aEEG seems to be a feasible technique for identifying infants at high risk of subsequent brain damage who might benefit from interventionist treatment after asphyxia[20].

The aEEG was predictive of an abnormal outcome with a sensitivity of 78% and specificity of 94%, positive predictive value of 85% and a negative predictive value of 92%.

LABORATORY INVESTIGATIONS

Neonatal asphyxia affects multiple organs, which needs to be evaluated as it affects the prognosis of HIE

AKI is common in perinatal asphyxia mostly in term babies. FENa and RFI are parameters used to assess the renal function and urinary β2M is a good biomarker for diagnosis and prognosis of acute tubular injury in babies with perinatal asphyxia[21].

Evaluation of blood urea and serum creatinine levels are used to assess the renal injury in HIE. Reduction in GFR occurs usually around 24 hours of life. The proximal renal tubule is affected the most. Urinary β2microglobulin could be used as a recent marker of kidney injury which signifies tubular dysfunction. Serum Cystatin C is a more sensitive marker of glomerular filtration rate than Cr in the newborns[22].

Markers of neuronal dysfunction are available to identify the CNS injury like Glial Fibrillary acid protein(GFAP) and ubiquitin carboxy terminal hydrolase L1(UCH-L1) expressed in neurons and astrocytes. Another marker S-100 β protein is found to be elevated in the first urine of HIE newborns[23].

Other markers associated with CNS injury are neuron specific enolase , brain derived neurotropic factor, interleukin -6 and creatinine kinase BB.

Management

A. Supportive care

1. Resuscitation. The 2011 Neonatal Resuscitation Program guidelines recommend initiating resuscitation with room air or blended oxygen with a targeted preductal Spo2 of 60–65% by 1 minute of life and 80–85% by 5 minutes of life in all term and preterm infants. There are no current guidelines specific to neonates with HIE. While resuscitation with 100% O2 more rapidly restores CBF and perfusion in animal studies, hyperoxia should be avoided, as oxidative damage from oxygen-free radicals can further exacerbate hypoxic ischemic brain injury.

2. Ventilation. Assisted ventilation may be required to maintain Pco2 within the physiologic range. While hypercarbia exacerbates cerebral intracellular acidosis and impairs cerebrovascular autoregulation, hypocarbia (Paco2 <20–25 mm Hg) decreases CBF and is associated with PVL in preterm infants and late-onset sensorineural hearing loss in full-term infants.

3. Perfusion. Arterial blood pressure should be maintained in the normotensive range for gestational age and weight. Due to the loss of cerebrovascular autoregulation, volume expanders and inotropic support should be used cautiously in order to avoid rapid shifts between systemic hypotension and hypertension.

Physiology of shock in perinatal asphyxia involves the release of endogenous catecholamines leading to normal or increased SVR clinically manifested by pallor, mottled appearance, and poor perfusion and myocardial dysfunction. The baby is likely to be euvolemic and may have associated pulmonary hypertension.

Cardiovascular stability and adequate mean systemic arterial blood pressure are important in order to maintain adequate cerebral perfusion pressure. Fluids, inotropes, vasopressors, and hydrocortisone replacement are used to treat shock in the neonate. Mainstay of shock management includes inotropes and vasopressor therapy.

1) Inotropes are used to improve cardiac function :

Sympathomimetic amines are commonly used in infants which includes Dopamine, Dobutamine and Epinephrine.

i. Dopamine activates receptors in a dose-dependent manner. At low doses (0.5 to 2 μg/kg/minute), dopamine has little effect on cardiac output. In

intermediate doses (5 to 9 μg/kg/minute), dopamine has positive inotropic and chronotropic effects. The increase in myocardial contractility depends in part on myocardial norepinephrine stores.

ii. Dobutamine is a synthetic catecholamine with relatively cardioselective inotropic effects. In doses of 5 to15 μg/kg/minute, dobutamine increases cardiac output with little effect on heart rate. Dobutamine can decrease SVR and its inotropic effects are independent of norepinephrine stores.

iii. Epinephrine has potent inotropic and chronotropic effects in the 0.05 to 0.3 μg/kg/minute doses. At these doses, it has greater β2-adrenergic effects in the peripheral vasculature with little α-adrenergic effect resulting in lower SVR. Epinephrine is an effective adjunct therapy to dopamine because cardiac norepinephrine stores are readily depleted with prolonged and high-rate dopamine infusions.

b. Milrinone is a phosphodiesterase-III inhibitor that enhances intracellular cyclic adenosine monophosphate content preferentially in the myocardium leading to increase in cardiac contractility. It improves diastolic myocardial function more readily than dobutamine. Milrinone also lowers pulmonary vascular resistance and SVR by increasing cAMP levels in vascular smooth muscle.

2. Vasopressor therapy is used to increase SVR and improve BP which will restore perfusion to vital organs.

a. Dopamine in high doses (10to 20 μg/kg/minute) causes vasoconstriction by releasing norepinephrine from stores and direct α-adrenergic receptors. Neonates have reduced releasable stores of norepinephrine.

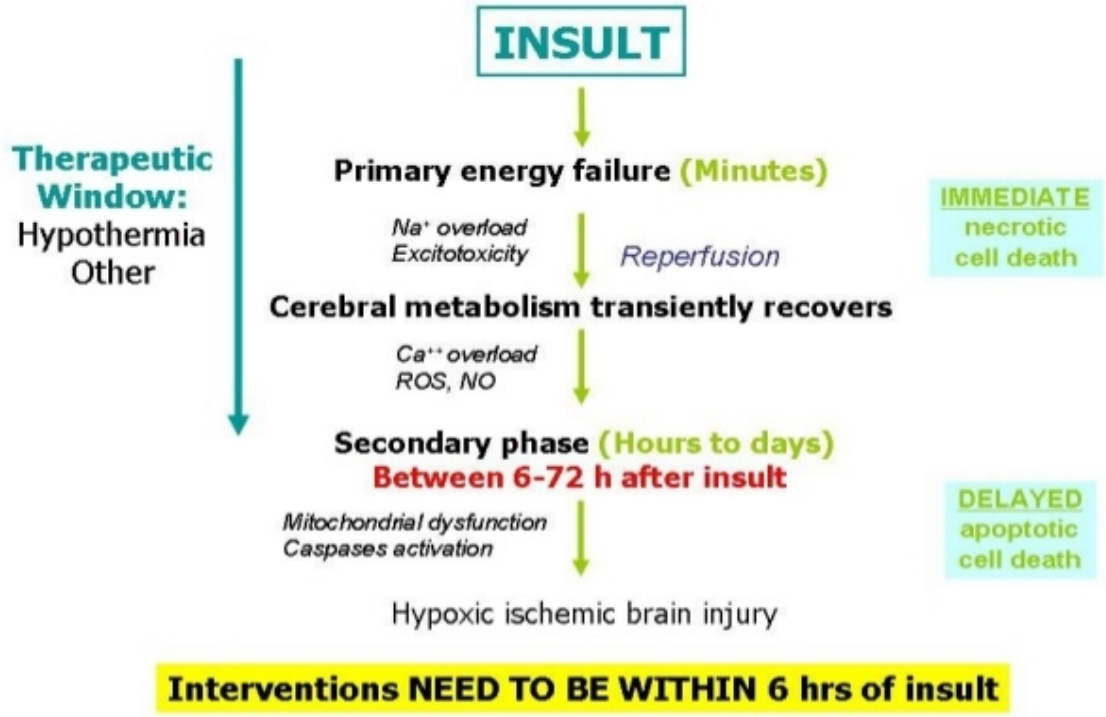
4. Acid-base status. The base deficit is thought to increase in the first 30 minutes of life due to an initial washout effect secondary to improved perfusion and transient increase in lactic acid levels. Acidosis normalizes in the majority of infants by 4 hours of life, regardless of bicarbonate therapy. The rate of recovery from acidosis is reflective of HIE severity but not duration, and is not predictive of outcomes. Sodium bicarbonate therapy is not recommended as it causes a concomitant rise in intracellular Pco2 levels, negating any changes in pH, and is associated with increased rates of intraventricular hemorrhage and mortality.

5. Fluid status. Initial fluid restriction is recommended as HIE infants are predisposed to a fluid overload state from renal failure secondary to acute tubular necrosis (ATN) and SIADH. The avoidance of volume overload helps avert cerebral edema. A single dose of theophylline (8 mg/kg) may be considered within the first hour to increase glomerular filtration by blocking adenosine mediated renal vasoconstriction.

6. Blood glucose. Initial hypoglycaemia (< 40 mg/dL) in the context of HIE amplifies the risk of progression from moderate to severe encephalopathy. Timely and frequent monitoring of blood glucose levels is therefore essential.

7. Seizures. Seizure activity is both a consequence and determinant of brain injury. A Cochrane review showed no reduction in death, neurodevelopmental disability, or combined outcome with the prophylactic use of anticonvulsant therapy. Phenobarbital therapy is recommended as the first-line agent for prolonged or frequent clinical seizures. The use of prophylactic phenobarbital in conjunction with hypothermia has shown a reduction in clinical seizures but not neurodevelopmental outcome. Phenobarbital levels in asphyxiated infants should be carefully monitored because hepatic and renal dysfunction, as well as hypothermia, can increase the drug's half-life and plasma concentration.

Figure 2



PHASES OF HYPOXIC ISCHEMIC ENCEPHALOPATHY

NEUROPROTECTIVE STRATEGIES IN PRETERM

Antenatal steroids, magnesium sulphate, delayed cord clamping, caffeine eythropoietin and melatonin.

IN TERM

Therapeutic hypothermia, erythropoietin, xenon, argon, stem cell therapy(umbilical cord stem cells, mesenchymal stem cells,embryonic stem cells induced pluripotent Stem cells, neuronal/amniotic fluid stem)

n-acetyl cysteine / allopurinol, magnesium, calcium channel blockers and anticonvulsants.

THERAPEUTIC HYPOTHERMIA:

Therapeutic hypothermia attenuates secondary energy failure by decreasing cerebral metabolism, inflammation, excitotoxicity, oxidative damage and cellular apoptosis. Hypothermia is now emerging as standard of care for perinatal asphyxia. Early identification of neonates with perinatal asphyxia and their timely referral to tertiary care centers for hypothermia therapy is therefore crucial. Hypothermia protocols that recommend temperature regulation prior to admission (such as passive cooling or active cooling on transport) are institution specific and must be clarified with the accepting facility at the time of referral. To date, 3 large multicenter trials of cerebral hypothermia for HIE, initiated within 6 hours of birth and continued for 72 hours, have been completed[24].

METHOD

Mild hypothermia initiated within 6 hours with a 33.5 degrees with a target oesophageal temperature goal (32.5-34.5 degrees) for 72 hours followed by Slow rewarming of 0.5 degree/2hrs untill 36.5(10 hrs).

The Total Body Hypothermia for Neonatal Encephalopathy (TOBY) TRIAL

In this trial babies are cooled to a body temperate of 33.5°C but used aEEG entrance criteria. Cooling did not reduce the combined rate of death or severe disability, but improved neurodevelopmental outcomes were seen among survivors.

Selective head cooling (SHC) increases the temperature gradient across the brain from the central to peripheral regions. This is in contrast to whole body cooling, which maintains a uniform temperature gradient across the brain. In a systematic review of 13 studies, systemic hypothermia, but not SHC, was associated with a reduction in outcomes of cognitive delay, psychomotor delay, and cerebral palsy. The reduction in mortality or neurodevelopmental disability among survivors was similar between both modes of cooling. There are no clinically significant adverse effects from therapeutic hypothermia, and the mode of cooling does not have any differential impact on multiorgan system dysfunction in asphyxiated infants [26].

FREE RADICAL SCAVENGERS

Allopurinol, desferrioxamine, vitamin E , C and N-Acetyl cysteine.

NMDA RECEPTOR BLOCKER

Magnesium, xenon and ketamine.

ERYTHROPOITIN

Hypoxia would promote upregulation of EPO receptor.when EPO available,promotes cell survival,when EPO absent,it leads to programmed cell death,Early benefits of EPO - anti apoptotic/anti-inflammatory and Late benefits -neurogenesis,plasticity,remodeling.

MELATONIN

N-ACETYL 5 METHOXY TRYPTAMINE.It is an Endogenous indolamine which crosses BBB. It functions as Antioxidant/anti apoptotic / antiinflammatory. The combination therapy with MELATONIN+TH-improves survival. This therapy shows better neurodevelopmental outcome at 6 months of age.

XENON

Xenon Crosses blood brain barrier and placenta and Binds to NMDA/GLUTAMATE receptors thereby Inhibiting excitatory function reduced lactate to N Acetyl aspartate ratio in MRS is a good predictive imaging marker of neurodevelopmental outcome.

UMBILICAL STEM CELLS

Contains mesenchymal stem cells/progenitor stem cells/UCB-MONONUCLEAR CELLS.UCB-MNC could differentiate into all type of mature celll-neural cells .umbilical stem cells have greater proliferative potential and Low antigenicity.

FUTURE OUTLOOK ON NEUROPROTECTION

1)Remote ischemic post conditioning

2)Targeting inflammation

3)Targeting autophagy

PREDICTORS OF LONG-TERM NEURODEVELOPMENTAL OUTCOME IN PERINATAL ASPHYXIA

Parameters	Outcome
1)Fetal acid base measurement	Umbilical artery pH < 7.1, Base deficit > 11 Major neurological deficits in 14%
2) Extended APGAR score	At 20 minutes < 3: CP in 57% survivors
3) Severity of the encephalopathy	Mild-no neurological sequelae Moderate-25% have neurological sequelae. Severe - 100% have neurological sequelae.
4) Seizures	- Early onset and refractory seizures
5) Elevated CPK BB	- > 5 IU
6)Oliguria	Persistently < 1 ml/kg/hr for the first 36 hours of life

7) Background EEG	Burst suppression pattern on any day. Isoelectric pattern on that day
8) Brainstem auditory, Visual and Somatosensory evoked potentials.	Abnormal latencies and amplitude ratios
9) Neurologic examination at At the end of first week	If abnormal, predicts long-term abnormality
10) head growth	If slow in the first month, is a poor Prognosis.

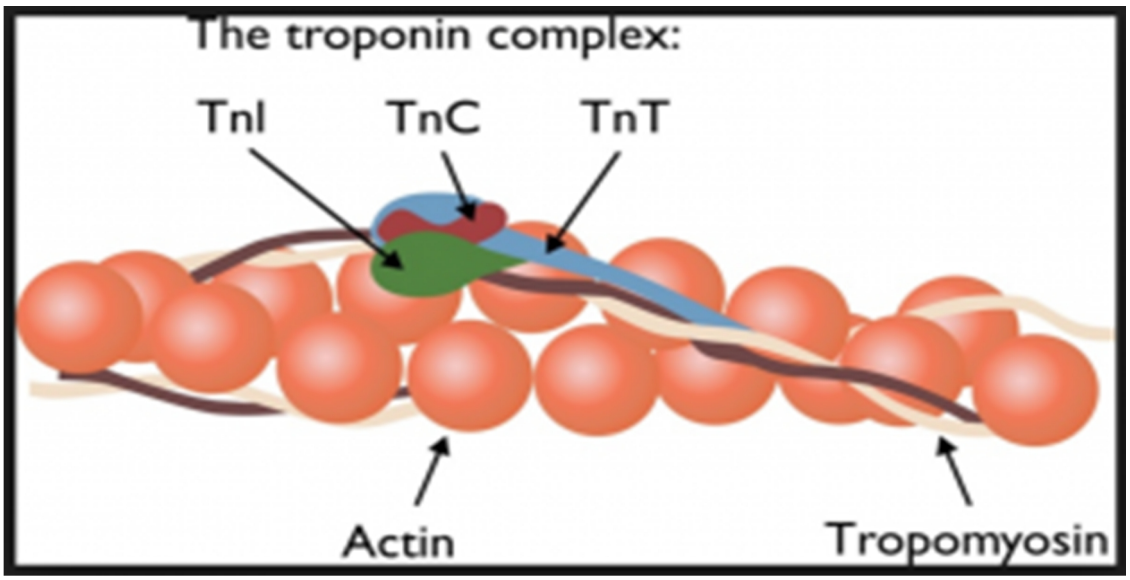
MARKERS OF HYPOXIC MYOCARDIAL INJURY - CARDIAC TROPONIN I

Cardiac biomarkers are used to identify cardiac dysfunction and failure in term and preterm infants. Cardiac troponins are used to assess cardiomyocyte compromise. Affected cardiomyocytes release troponin into the bloodstream, resulting in elevated levels. Cardiac troponins are suggested as potential biomarkers in the diagnosis and treatment of neonatal disease complicated by circulatory compromise[26].

Creatine kinase-MB (CK-MB) and the cardiac troponins I and T (cTnI and cTnT) are the biochemical markers used to evaluate myocardial dysfunction. CK-MB levels are elevated in newborns after perinatal and neonatal hypoxia-ischemia, but this elevation is not specific enough to be of clinical value[27,28].

Troponin is an inhibitory protein complex located on the actin filament in all striated muscles and consists of three subunits: T, C, and I[29] .Cardiac troponin I (cTnI) was measured as an indicator of cardiac injury ,but now used to predict neonatal outcome in perinatal asphyxia . cTnI is the subunit that inhibits actinomyosin ATPase activity, thereby preventing muscle contraction in the absence of Ca^{2+} and blocking the formation of actin-myosin bridges. It is also considered a highly specific indicator of myocardial injury in adults[30].

Figure 3



TROPONIN I PROTEIN COMPLEX

cTnI is released into the bloodstream after myocardial damage and for this reason, cTnI has been used as a marker of myocardial injury[31]. cTnT and cTnI have been proposed to be biochemical indices of myocardial injury in neonates with asphyxia, respiratory distress syndrome

(RDS) , and septic or cardiogenic shock. TROPONIN I gets elevated with 2-4 hours of myocardial injury. The half-life of cTnI is relatively short (90 min), its diagnostic time range from a few hours to 10-14 days after the episode of myocardial injury [29].

Conditions other than asphyxia which shows increased troponin levels are Respiratory distress syndrome, PDA, sepsis/NEC, Growth Retardation and Preeclampsia. It could be used in diagnosis and for determining long term outcome in many of these diseases[32].

Normally Troponin I is higher in newborns. Its due to cardiorespiratory compromise associated with adaptation to postnatal circulation. Normal value in adults is <0.01ng/ml. where as in infants normal value is considered to be <0.1 ng/ml.In newborns normal range of Troponin I is 0.63 ± 0.58ng/ml with a range of 0.001 - 4.3ng/ml. 1.8 ng/ml is considered the upper limit of normal value[29].

Perinatal asphyxia not only affects CNS , but leads to multi organ dysfunction the severe would be the cardiac dysfunction. Ischemia and myocardial necrosis occurs in 25-51% of newborns[33]. The incidencs of cardiac dysfunction accounts about 40 % in perinatal asphyxia. Apart from clinical indicators of myocardial injury like ECG and ECHO[34], there is a need for early prediction of myocardial dysfunction for which Troponin I

levels would be more useful as it serves as both early predictor of myocardial injury and outcome of HIE.

MATERIALS AND METHODS

SUBJECT SELECTION

Term asphyxiated babies with APGAR score of <7 at first minute of life as per WHO PERINATAL NEONATAL DATA BASE.

DURATION OF STUDY

One year from MARCH 2017 to FEBRAURY 2018.

SAMPLE SIZE

50 asphyxiated term babies admitted in SNCU of tertiary care centre- Tirunelveli Medical College Hospital.

TYPE OF STUDY

Prospective COHORT study of term asphyxiated babies admitted in SNCU in a tertiary care centre.

INCLUSION CRITERIA

1) Term babies (>37 weeks)-as determined by gestational scoring by NEW BALLARD'S SCORE

2) Birth weight of >2 .5 kg.

3) Asphyxiated term babies with APGAR SCORE of < 7 at first minute as per WHO PERINATAL NEONATAL DATA BASE

EXCLUSION CRITERIA

1) Congenital Heart Disease.

2) Babies with congenital anomalies.

3) Sepsis

4) Multiple pregnancy

5) Respiratory Distress Syndrome.

6) IUGR babies.

7)Preeclampsia.

LABORATORY ASSESSMENT

Parameter-cardiac **TROPONON I**

Normal value **- 0.63 (± 0.58)ng/ml**

Sample - **serum**

Timing of sampling - **within 6 hrs of life**

Method-**QUANTITATIVE CHEMILUMINESCENCE ASSAY**

Following PARAMETERS are included and monitored in the present study .

1. Gravida
2. Gestational age
3. Mode of delivery
4. Sex
5. Birth weight
6. Seizures
7. Shock
8. Duration of inotropic support
9. Ventilator support
10. Renal parameter
11. Troponin I
12. Electocardiogram
13. Echocardiogram
14. Cranial ultrasound.

METHODOLOGY

This study was approved by ethical committee of our institute. 50 neonates born in TVMCH with birth asphyxia as defined by an APGAR score of <7 @ one minute of life, whose parents gave written informed consent were enrolled for the study. Prestructured proforma was used to obtain information from mother and to monitor & record the parameters.

Information regarding birth order, gestational age ,sex and birth weight were recorded in the proforma.

Clinical features including presence of seizures within 24 hours, shock, inotropes ,duration of inotropic support and ventilator support requirement were monitored .

Laboratory investigations.

RBC count (Normal-5.8million /cu.mm, low <5 million /cu.mm)

WBC count (Normal 9000 - 30,000 leukopenia < 9000, leucocytosis > 30,000).

RFT-urea (normal 2-19 mg/dl, high >19 mg/dl).

Serum Creatinine (normal 0.3-1 mg/dl and high > 1 mg/dl).

Troponin I is 0.63 ± 0.58ng/ml with a range of 0.001 - 4.3ng/ml. 1.8 ng/ml is considered the upper limit of normal value[29].

ECG and ECHO taken at 24 and 48 hours of life.

ECG Abnormalities-T wave inversion, ST depression / elevation were included in the study.

ECHO - decreased left ventricular contractility, elevated left ventricular end diastolic pressure, Tricuspid Regurgitation & pulmonary hypertension were analysed and included in the study.

CRANIAL ULTRASOUND

Presence of edema as loss of grey-white differentiation, small ventricles, intracranial haemorrhage and increased periventricular echogenicity in asphyxiated newborns is included in the study .

Finally all parameters were entered in the Microsoft excel sheet and statistical analysis was performed. The Troponin I levels was compared with the of baseline parameters(gravida,gestational age, birth weight, sex ,mode of delivery) HIE severity,ECG changes,ECHO ,presence of shock , inotropic support and finally with the outcome of HIE.

50 asphyxiated newborns were included in the study. The study group included neonates with APGAR SCORE of < 7 at first minute of life as per WHO neonatal database and grouped into HIE I,II and III based on SARNAT SARNAT staging done at 24 hours of life.

HIE I -20 neonates

HIE II-12 neonates

HIE 3 -18 neonates

SPSS software version 21.0 was used to do this statistical analysis.

Following tests were used to compare the mean-T TEST & ANOVA were used.

For comparing relation between groups-CHI SQUARE AND KRUSKAL WALLIS TEST were used.

Gestational age, sex, birth order, mode of delivery, birth weight ,renal parameters were compared with HIE staging and Troponin I levels to assess the severity of HIE.

Shock, duration of inotropic support, ECG,ECHO – all 4 parameters were used to compare the severity of myocardial injury with elevated troponin I levels.

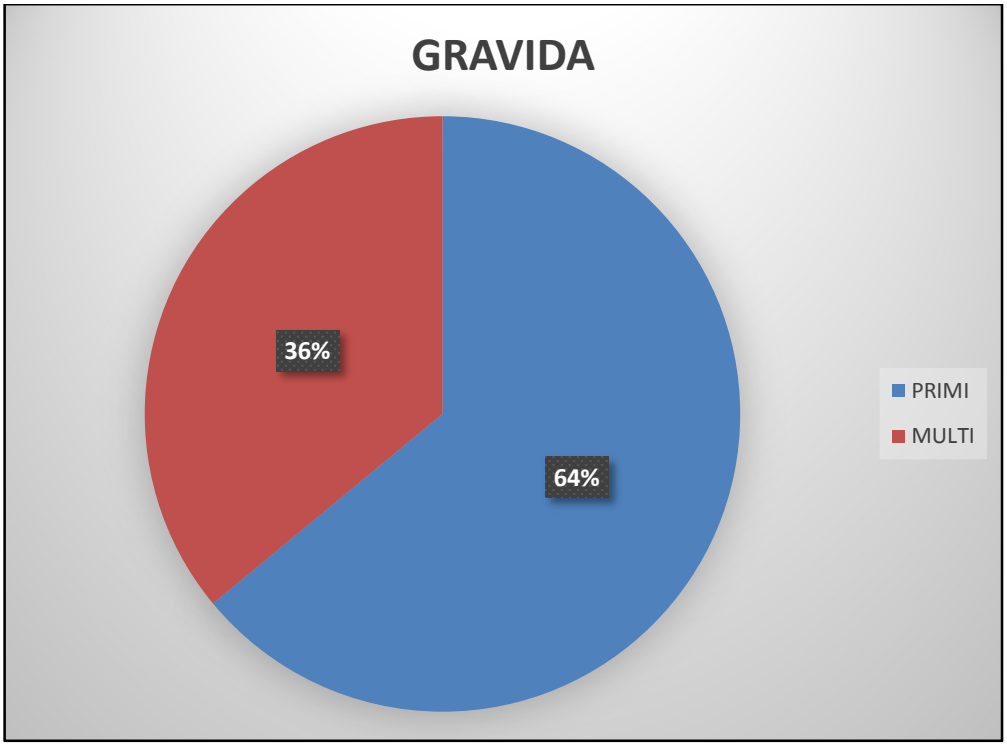
Seizures, ventilator support, cranial USG were compared with troponin I levels to assess the severity of HIE and troponin I levels

STATISTICAL ANALYSIS

Among the 50 asphyxiated neonates, collected data and monitored parameters were entered in Microsoft excel sheet and values were analysed with regards to correlation between troponin I levels ,HIE severity and early prediction of myocardial dysfunction by troponin I levels.

RESULTS

Figure 4



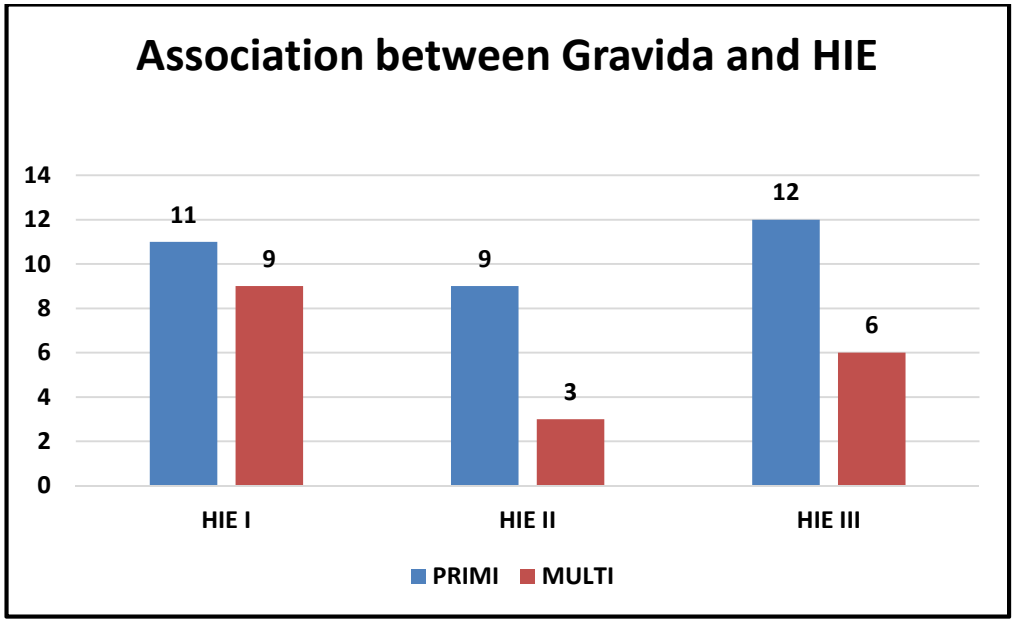
Distribution based on gravida among HIE Neonates

Table No : 1

Association between Gravida and HIE

GRAVIDA VS HIE(n=50)				
GRAVIDA	HIE I	HIE II	HIE III	TOTAL(%)
PRIMI	11	9	12	32(36)
MULTI	9	3	6	18(64)
TOTAL	20	12	18	50
KRUSKAL WALLIS TEST				
P VALUE - 0.499				

Figure 5



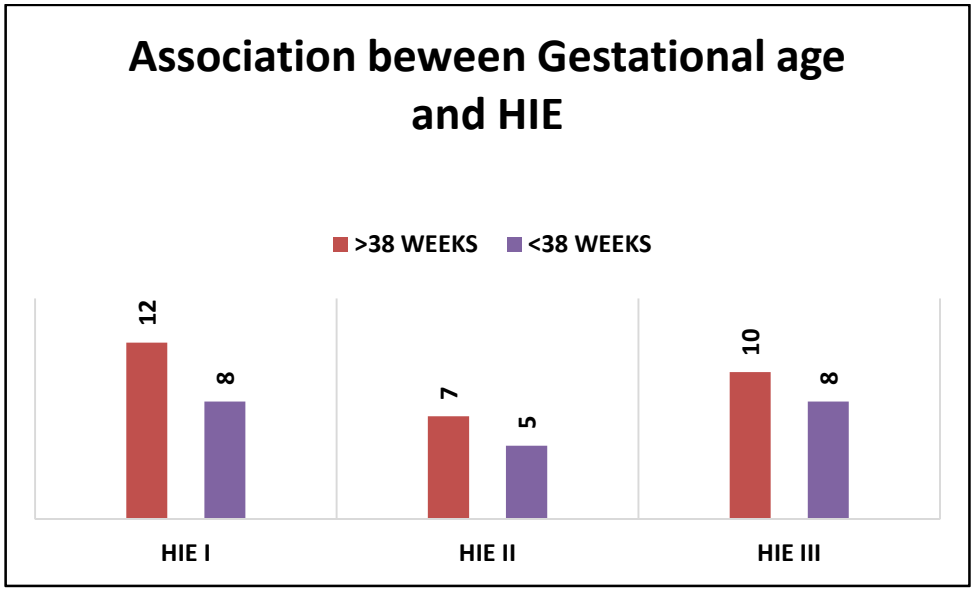
On comparing the gravida and HIE severity the P value was not statistically significant ,which signifies no correlation between parity and HIE severity.

Table No:2

Association between Gestational age and HIE(n=50)				
GESTATIONAL AGE	HIE I	HIE II	HIE III	TOTAL(%)
>38 WEEKS	12	7	10	29(58)
37-38 WEEKS	8	5	8	21(42)
TOTAL	20	12	18	50
KRUSKAL WALLIS TEST				
P VALUE - 0.961				

The p value was not significant when comparing gestational age and HIE which shows that gestational age has no impact on severity of HIE.

Figure 6



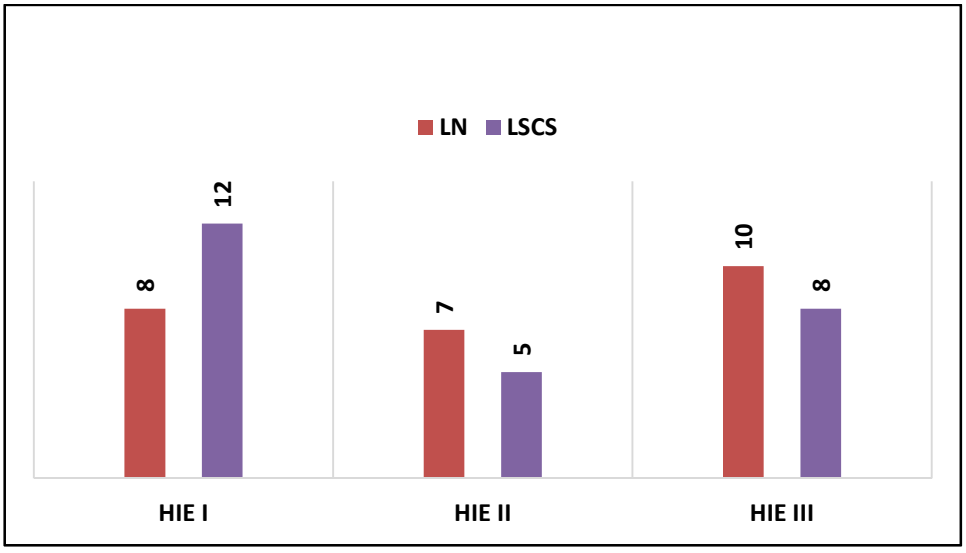
MODE OF DELLIVERY

Table No: 3

Association between Mode of Delivery and HIE (n=50)				
MODE OF DELIVERY	HIE I	HIE II	HIE III	TOTAL(%)
LN	8	7	10	25(50%)
LSCS	12	5	8	25(50%)
TOTAL	20	12	18	
KRUSKAL WALLIS TEST				
P VALUE – 0.507				

Figure 7

Association between Mode of Delivery and HIE



As the P VALUE was not significant this implies that mode of delivery has no impact in severity of HIE.

Table No:4

SEX DISTRIBUTION AMONG HIE(n=50)				
SEX	HIE I	HIE II	HIE III	TOTAL(%)
MALE	11	7	10	28(44)
FEMALE	9	5	8	22(56)
TOTAL	20	12	18	50
KRUSKAL WALLIS TEST				
P VALUE – 0.982				

Correlation between HIE severity and sex was compared by KRUSKAL WALLIS TEST which did not show statistical significance,Which shows sex has no impact on severity of HIE.

Figure 8

Sex Distribution Among HIE

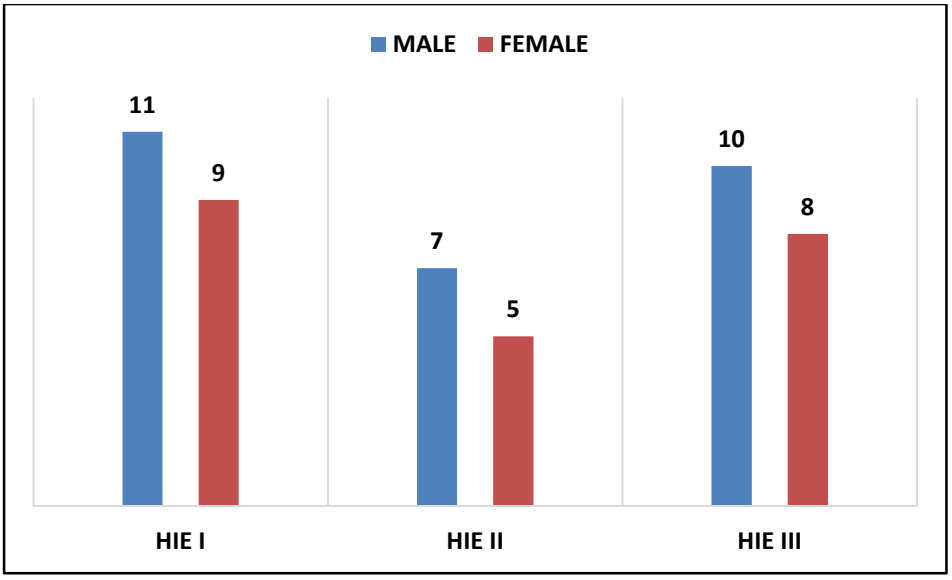


Table No: 5

ASSOCIATION BETWEEN BIRTH WEIGHT AND HIE(n=50)				
BIRTH WEIGHT	HIE I	HIE II	HIE III	TOTAL (%)
MORE THAN 3 KG	12	8	14	34(68)
2.5 to 3 KG	8	4	4	16(32)
TOTAL	20	12	18	50
KRUSKAL WALLIS TEST				
P VALUE - 0.499				

P value showed no statistical significance when birth weight and severity of HIE was compared which implies no correlation between HIE and Birth Weight.

Figure 9

Association between Birth weight and HIE

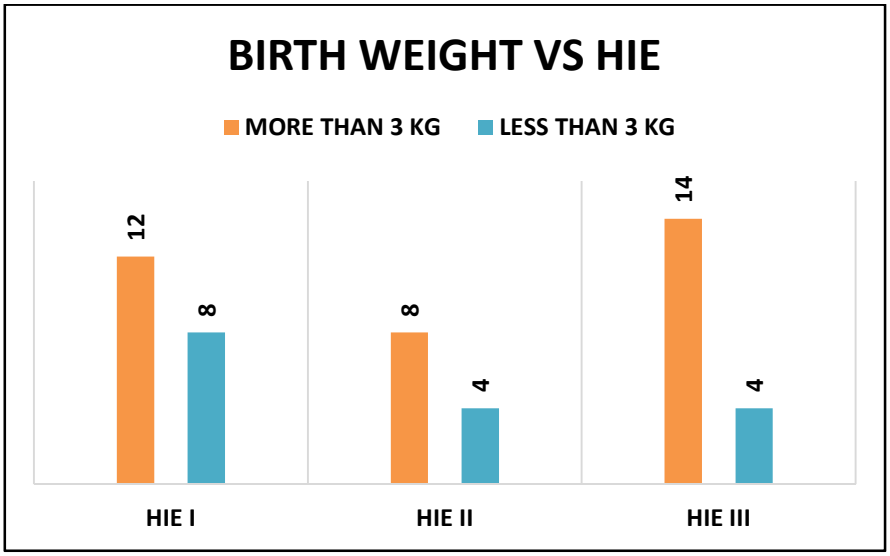


Table No :6

Association between Gravida, Gestational age, Mode of delivery,sex,Birth weight and Troponin I levels.

FACTORS	CATEGORY	TROPONIN I		P VALUE
		ELEVATED	NORMAL	
GRAVIDA	PRIMI	17	12	0.077
	MULTI	7	14	
GESTATIONAL AGE	>38WEEKS	12	18	0.165
	37-38 WEEKS	12	8	
MODE OF DELIVERY	LN	14	11	0.257
	LSCS	10	15	
SEX	MALE	13	12	0.981
	FEMALE	11	14	
BIRTH WEIGHT	>3 KG	22	19	0.087
	2.5 - 3KG	2	7	

The baseline data like Gravida,Gestational Age,Mode of Delivery,Sex and Birth weight when compared with Troponin I levels did not show statistical significance ,which implies the above mention factors have no association with Troponin I levels.

Table No: 7

SEIZURE DISTRIBUTION AMONG STUDY POPULATION

SEIZURES	NO OF PATIENTS	PERCENTAGE
YES	26	52%
NO	24	48%

Among 50 neonates ,26 out of 50 babies (52%) had seizures and 24 out of 50 babies (48%)had no seizures.

Table No:8

SEIZURE DISTRIBUTION AMONG HIE (n=50)				
SEIZURES	HIE I	HIE II	HIE III	TOTAL(%)
YES	-	10	16	26(52)
NO	20	2	2	24(48)
TOTAL	20	12	18	50
KRUSKAL WALLIS TEST				
P VALUE - 0.001				

Among HIE II babies,10 out of 12 had seizures and 16 out of 18 among HIE III babies had seizures. P VALUE was statistically significant which implies seizures has great impact on HIE severity.

Figure 10

Seizure Distribution among HIE

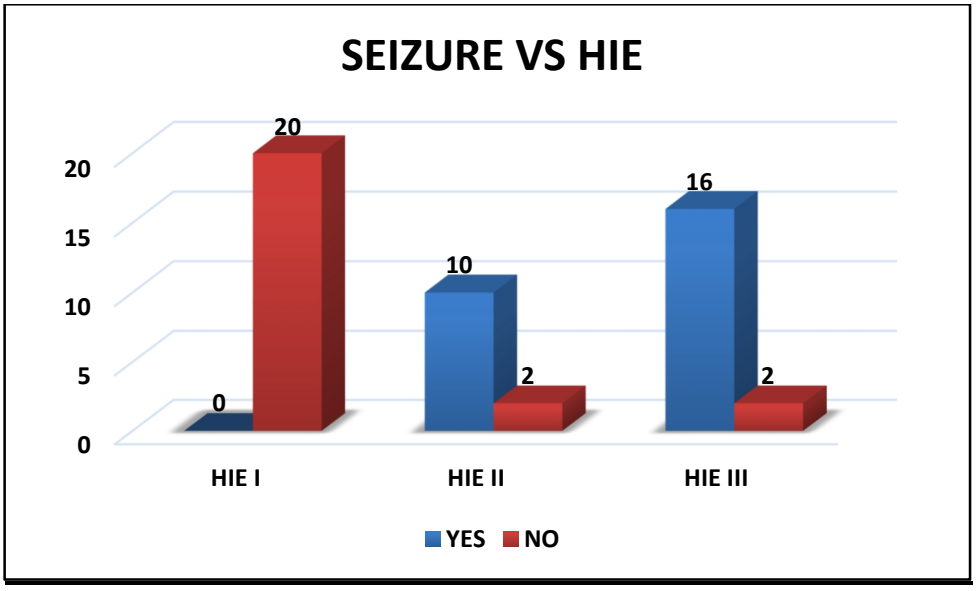


Table No:9

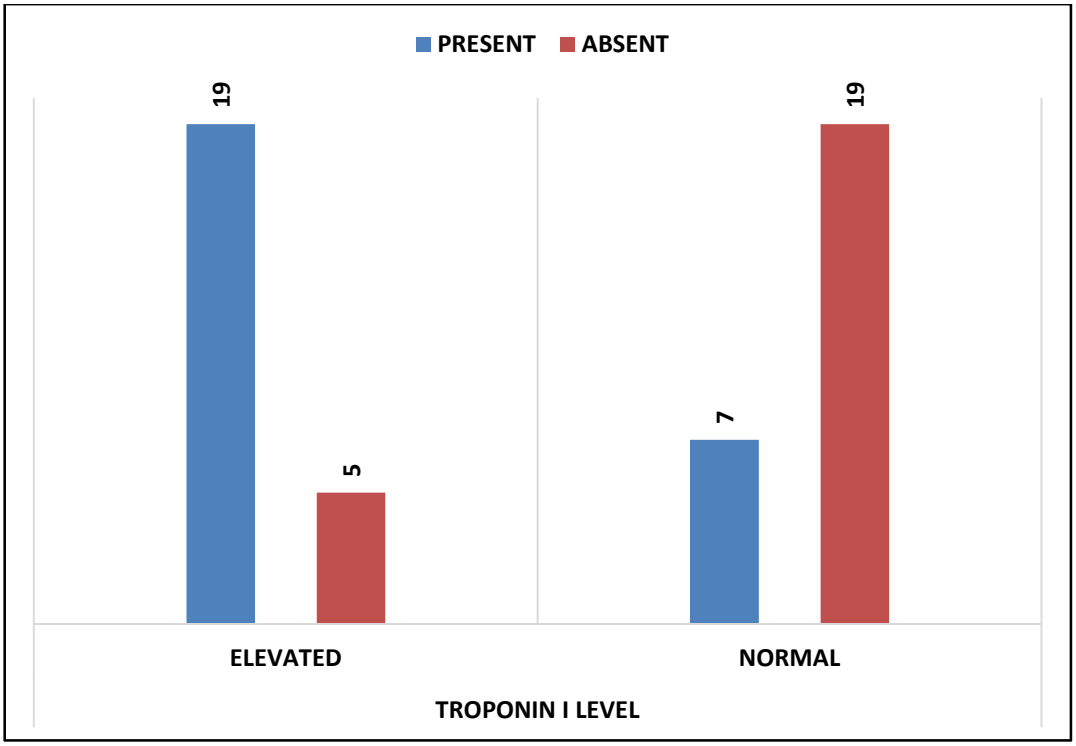
Association between seizures and Troponin I levels

SEIZURES	TROPONIN I LEVEL (n=50)	
	ELEVATED (%)	NORMAL (%)
PRESENT	19(79)	7(26)
ABSENT	5 (21)	19(74)
TOTAL	24	26
CHI SQUARE TEST		
P VALUE - 0.002		

Elevated troponin I and presence of seizures shows significant correlation with a P VALUE of 0.002, which shows that presence of seizures was more among elevated Troponin I Babies .

Figure 11

Association between seizures and Troponin I levels



Seizures was present in 19 out of 24 babies with elevated Troponin I levels and 7 out of 26 babies with normal Troponin I levels had seizures.

Table No:10

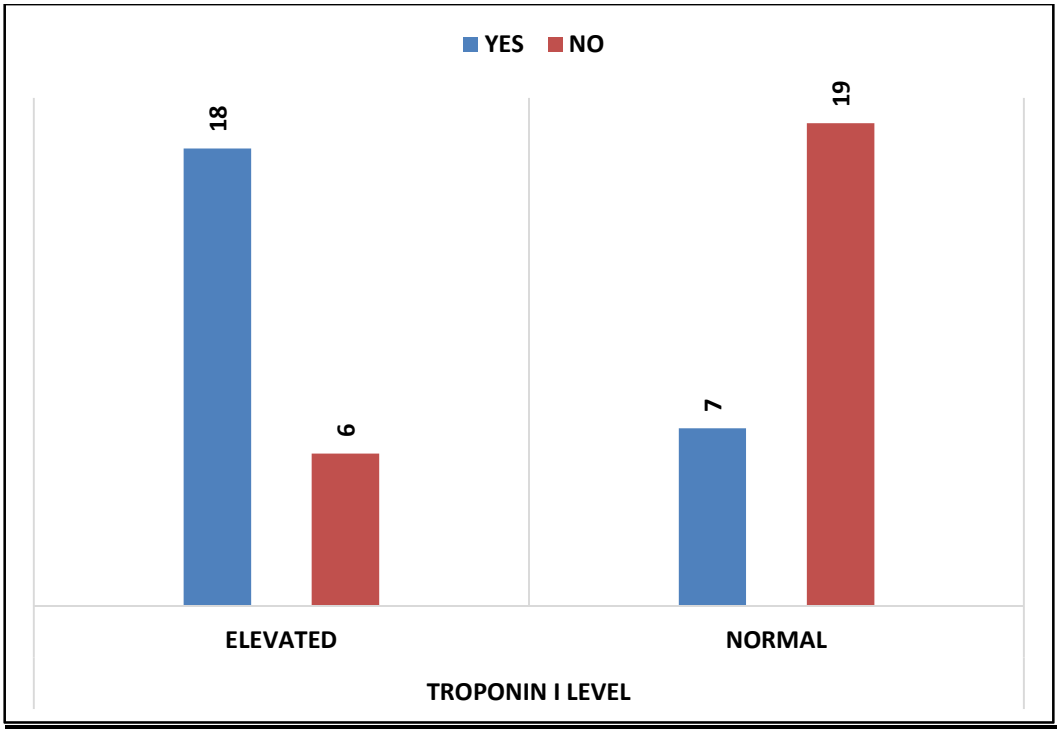
ASSOCIATION BETWEEN VENTILATOR REQUIREMENT AND TROPONIN I

VENTILATOR REQUIREMENT	TROPONIN I LEVEL	
	ELEVATED (%)	NORMAL (%)
YES	18(75)	7(26)
NO	6(25)	19(74)
TOTAL	24	26
CHI SQUARE TEST		
P VALUE - 0.006		

Correlation of ventilator requirement with elevated troponin I, shows a positive result with a significant P VALUE of 0.006,which implies that elevated Troponin I has significant correlation with severity of HIE(ventilator requirement) .

Figure 12

Association between Ventilator requirement and Troponin I



Among the 50 asphyxiated babies,18 out of 24 babies with elevated Troponin I levels required ventilator support and 7 out of 26 babies with normal Troponin I levels required ventilator support.

Table No:11

Association between shock and Troponin I levels

SHOCK	TROPONIN I LEVEL(n=50)	
	ELEVATED (%)	NORMAL (%)
PRESENT	22(91)	5(%)
ABSENT	2(9)	21(%)
TOTAL	24	26
CHI SQUARE TEST		
P VALUE - 0.001		

Shock with Troponin I showed a highly significant correlation with a P VALUE of 0.001 suggesting that elevated troponin I level correlates with presence of shock.

Figure 13

Correlation between shock and Troponin I levels

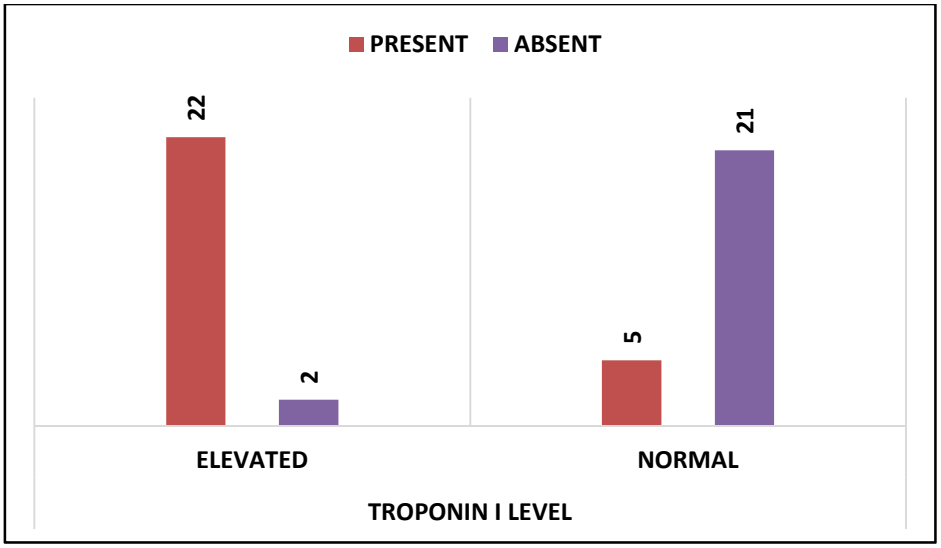


Table No:12

INOTROPE REQUIREMENT AMONG STUDY POPULATION

INOTROPES	NO OF PATIENTS	PERCENTAGE
REQUIRED	27	54%
NOT REQUIRED	23	46%

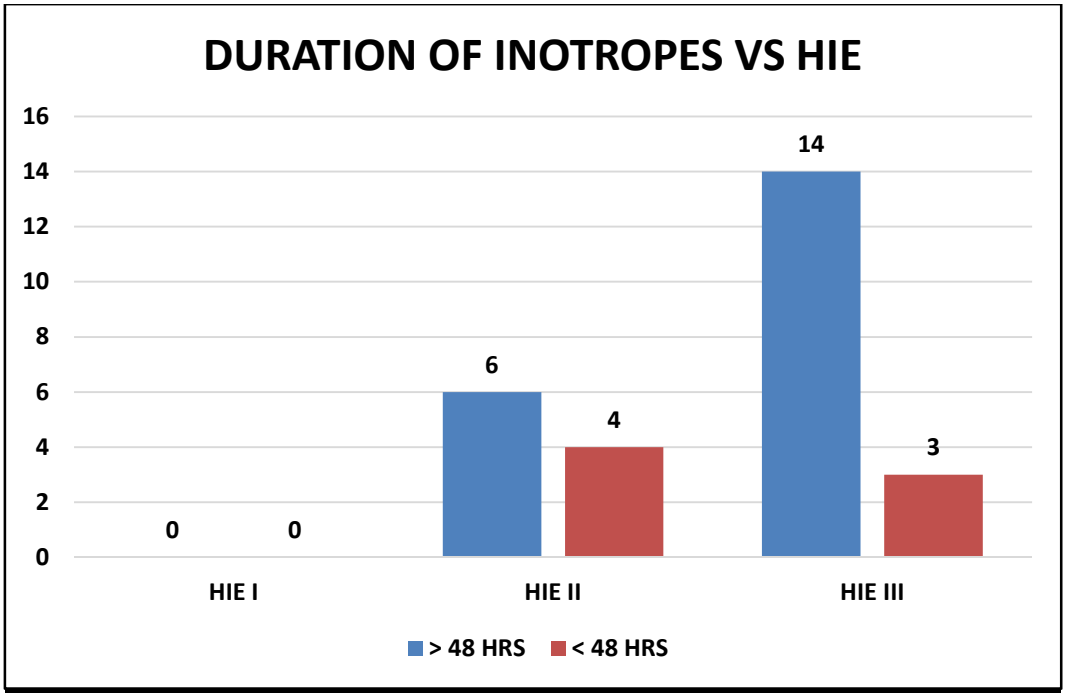
Among the 50 asphyxiated babies, 27 out of 50 babies required inotropes and 23 out of 50 babies did not require inotropes.

Table No:13

ASSOCIATION BETWEEN INOTROPE DURATION AND HIE (n=27)			
DURATION OF INOTROPES	HIE I	HIE II	HIE III
> 48 HRS	0	6	14
< 48 HRS	0	4	3
TOTAL	-	10	17
KRUSKAL WALLIS TEST			
P VALUE - 0.035			

Figure 14

Association between inotropes duration and HIE



Duration of inotropic support was compared with severity of HIE. This analysis showed a positive correlation with a P VALUE .035, which shows statistical significance between duration of inotropic support and HIE.

Table No:14

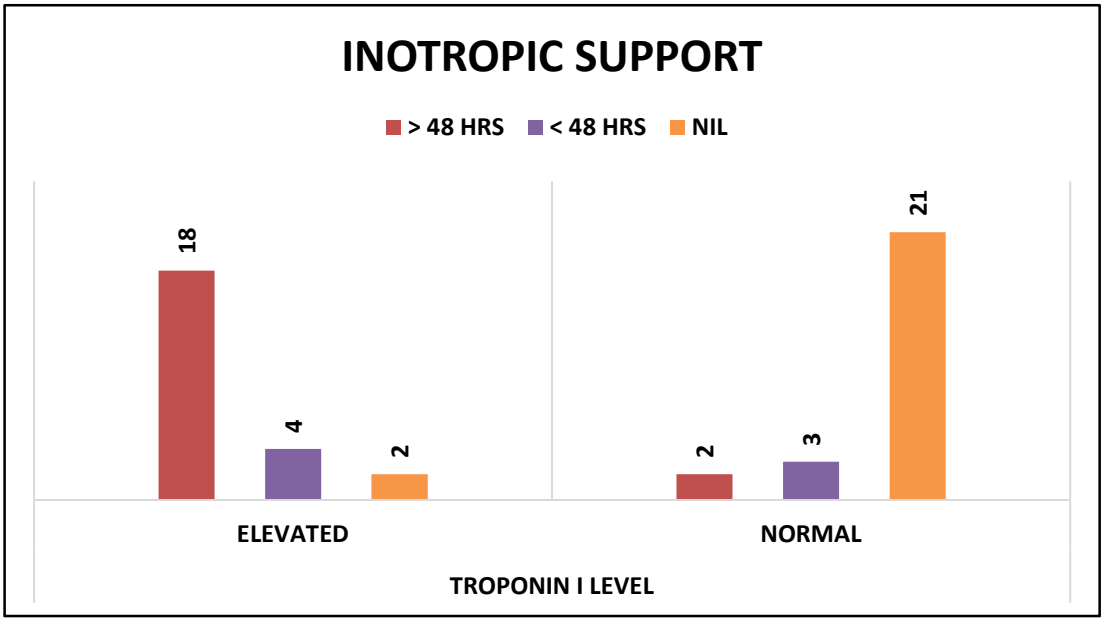
CORRELATION BETWEEN INOTROPE DURATION AND TROPONIN I LEVEL

INOTROPIC SUPPORT	TROPONIN I LEVEL (n=50)	
	ELEVATED	NORMAL
> 48 HRS	18	2
< 48 HRS	4	3
NIL	2	21
TOTAL	24	26
KRUSKAL WALLIS TEST		
P VALUE - 0.001		

Duration of inotropic support correlates significantly with troponin I level with a P value of 0.001,which implies babies with elevated troponin I levels has more impact on duration of inotropic support and myocardial dysfunction.

Figure 15

Correlation between inotrope duration and troponin I level



The babies with elevated Troponin I levels required inotropes for longer duration, when compared to babies with normal Troponin I levels.

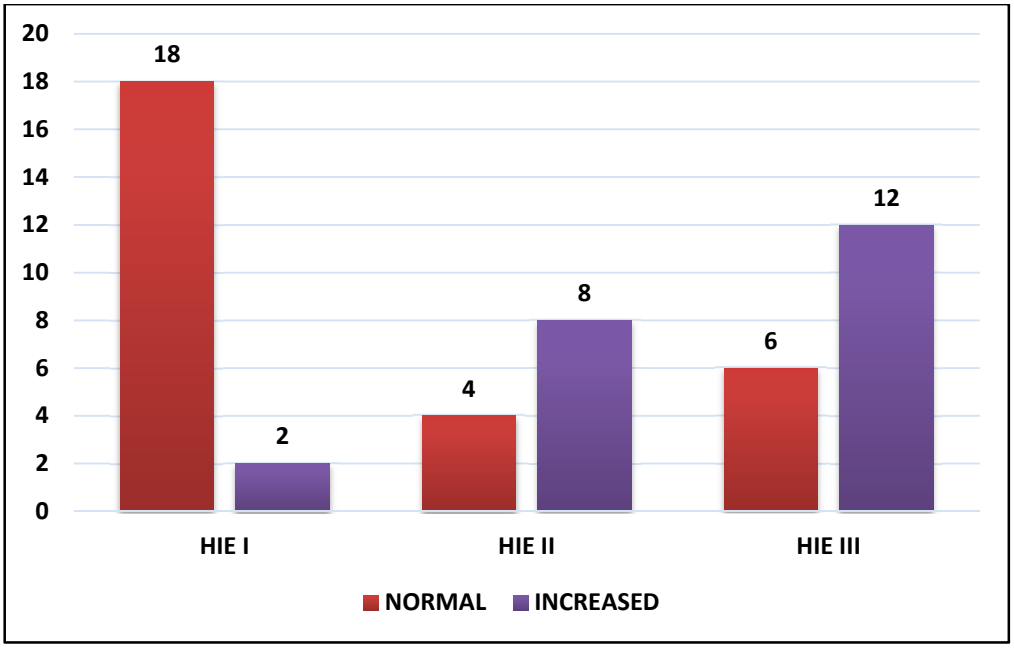
Table No:15

ASSOCIATION BETWEEN RENAL PARAMETERS AND HIE (n=50)				
RENAL PARAMETER	HIE I	HIE II	HIE III	TOTAL (%)
NORMAL	18	4	6	28(56)
INCREASED	2	8	12	22(44)
TOTAL	20	12	18	50
KRUSKAL WALLIS TEST				
P VALUE – 0.004				

Abnormal Renal parameters shows a statistical significant correlation with HIE severity.

Figure 16

Association between Renal parameters and HIE



Elevated renal parameters were comparable with HIE severity with a Significant P value of 0.004.

Table No:16

ECG ABNORMALITY AMONG STUDY POPULATION

ECG	NO OF PATIENTS	PERCENTAGE
NORMAL	23	46%
ABNORMAL	27	54%

Figure 17

ECG ABNORMALITY AMONG STUDY POPULATION

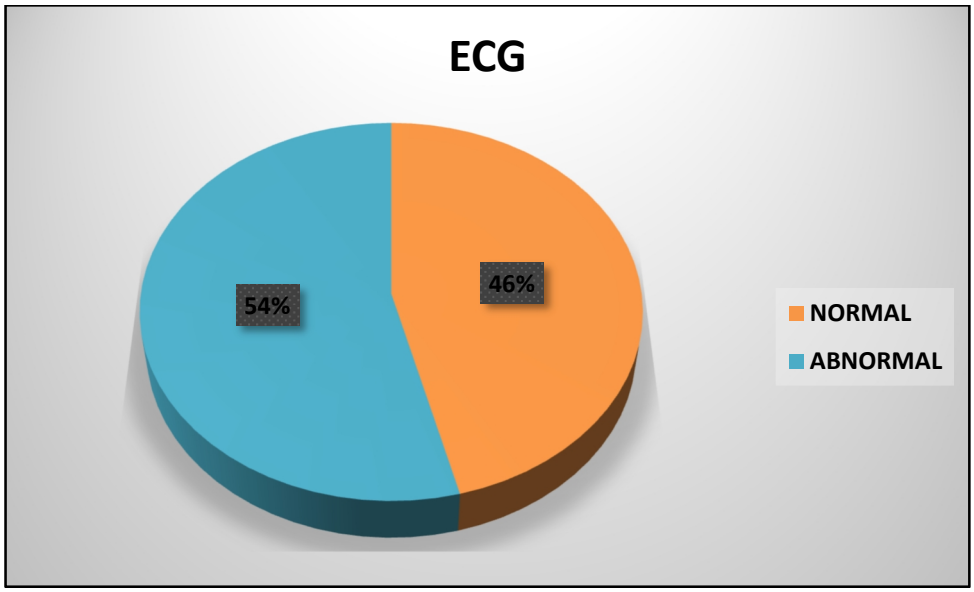


Table No:17

ASSOCIATION BETWEEN ABNORMAL ECG AND HIE(n=50)			
ECG	HIE I	HIE II	HIE III
NORMAL	17	3	3
ABNORMAL	3	9	15
TOTAL	20	12	18
KRUSKAL WALLIS TEST			
P VALUE - 0.03			

Among the 23 babies (46%) with abnormal ECG 15 are from HIE III,9 from HIE II AND 3 from HIE I. Abnormal ECG and HIE severity shows significant positive correlation with a P VALUE – 0.03.

Figure 18

Association between Abnormal ECG and HIE

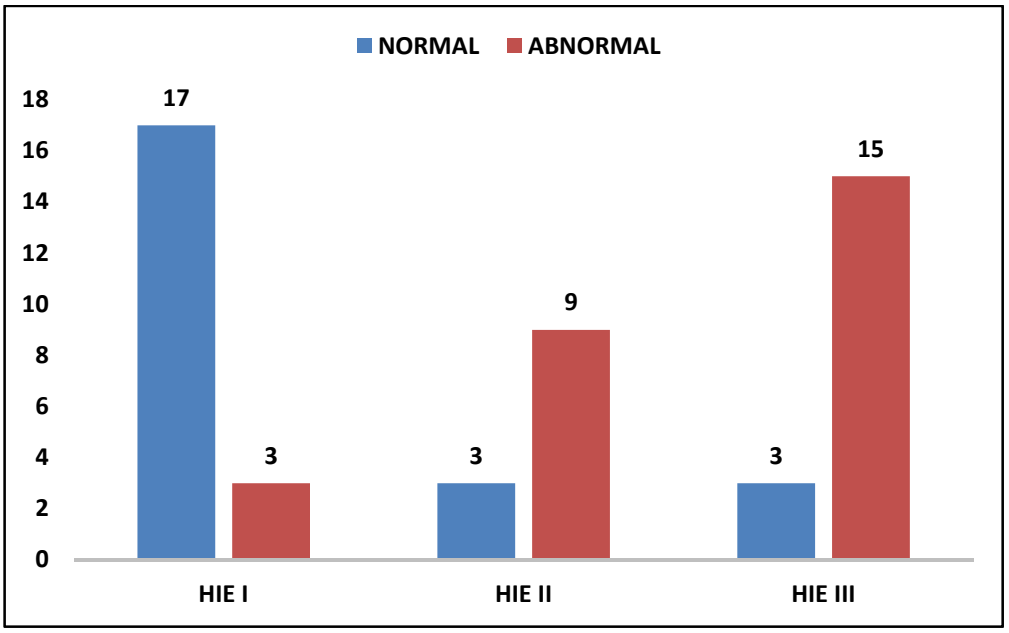


Table No:18

MEAN TROPONIN I LEVELS AMONG ABNORMAL ECG GROUP

	TROPONIN I LEVEL	
ECG	MEAN	SD
ABNORMAL	3.1	1.25
NORMAL	0.65	0.67
UNPAIRED T TEST		
P VALUE - 0.001		

The distribution between the mean of ECG and TROPONIN I levels were compared, which showed a significant P VALUE OF 0.001.

Figure 19

MEAN TROPONIN I LEVELS AMONG ABNORMAL ECG GROUP

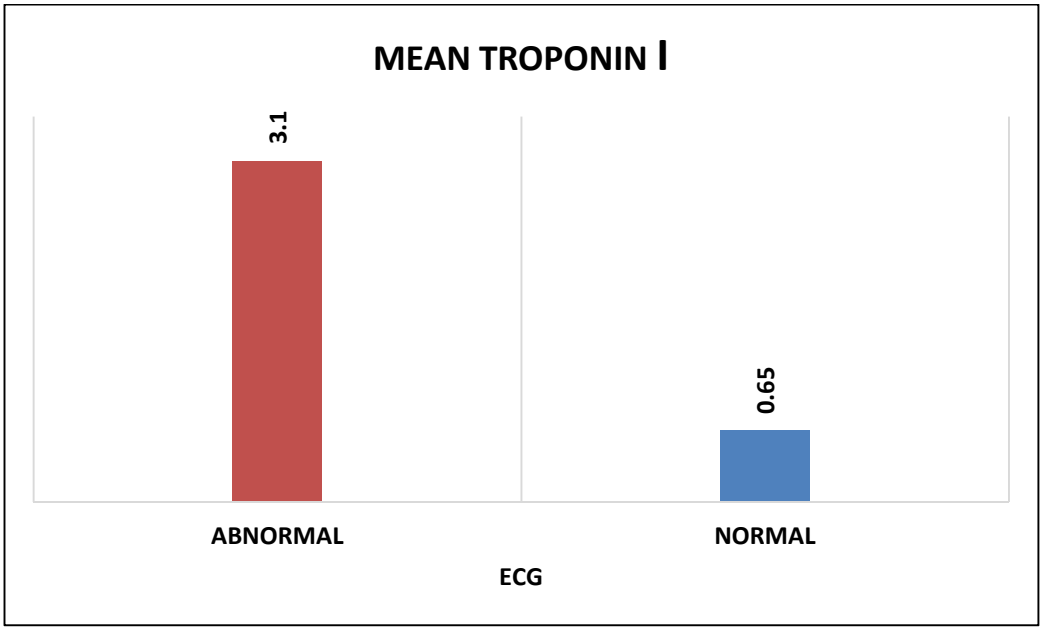


Table No:19

ASSOCIATION BETWEEN ABNORMAL ECHO AND HIE

ECHO VS HIE(n=50)					
ECHO	HIE I	HIE II	HIE III	TOTAL	PRECENTAGE
NORMAL	17	4	3	24	48%
ABNORMAL	3	8	15	26	52%
KRUSKAL WALLIS TEST					
P VALUE - 0.001					

ECHO VS HIE showed a significant positive correlation with a P VALUE -0.001

Figure 20

ASSOCIATION BETWEEN ABNORMAL ECHO AND HIE

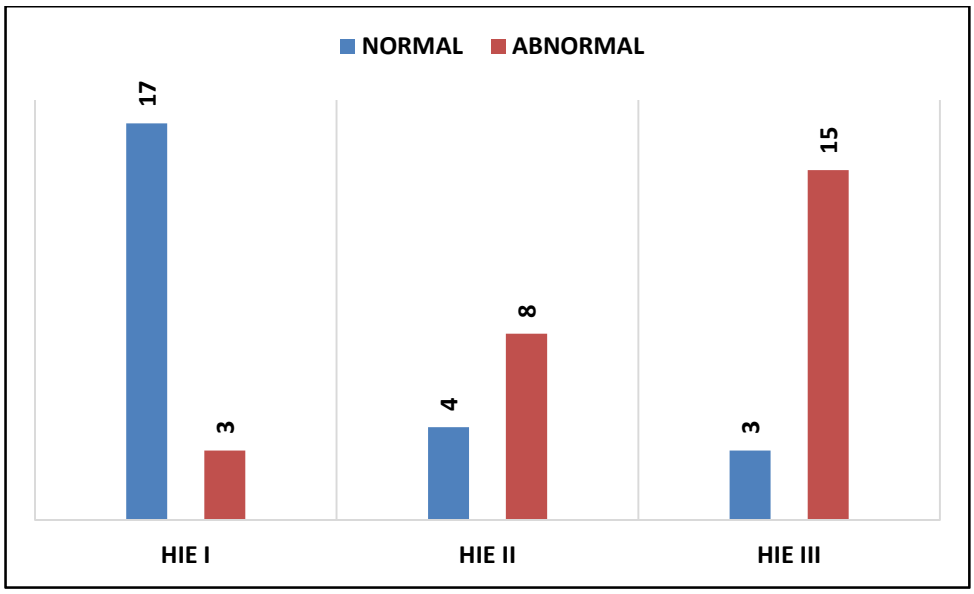


Table No:20

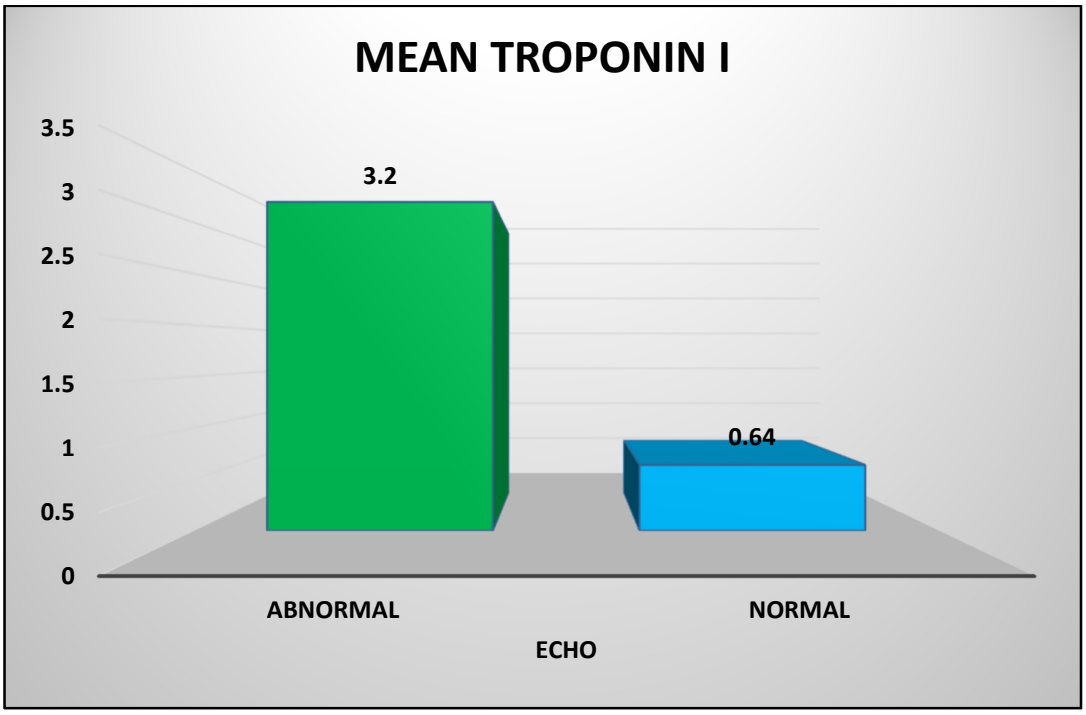
MEAN TROPONIN I LEVELS IN BABIES WITH ABNORMAL ECHO

	TROPONIN I LEVEL	
ECHO	MEAN	SD
ABNORMAL	3.2	1.16
NORMAL	0.64	0.66
UNPAIRED T TEST		
P VALUE - 0.001		
SIGNIFICANT		

Elevated troponin I levels was comparable with abnormal ECHO,When the mean was compared, showed a statisticaly significant correlation with a P VALUE of 0.001.

Figure 21

Mean Troponin I levels in babies with Abnormal ECHO



The mean Troponin I levels was 3.2ng/ml in babies with abnormal ECHO and the mean Troponin I levels was 0.54ng/ml in babies with normal ECHO.

Figure 22

Distribution of Abnormal Cranial USG Among HIE

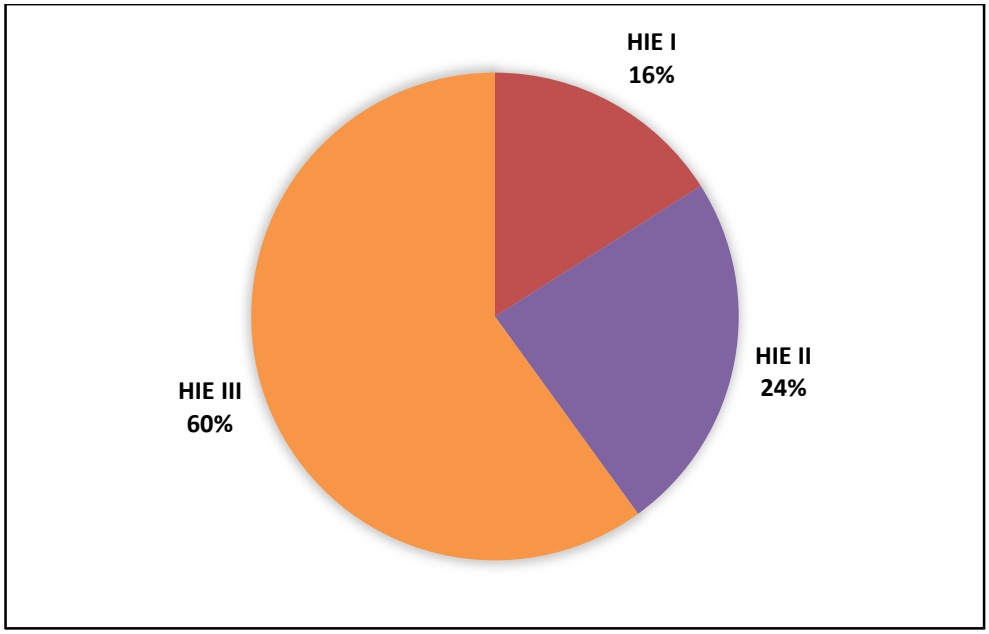


Figure 23

Association between Abnormal cranial USG and HIE

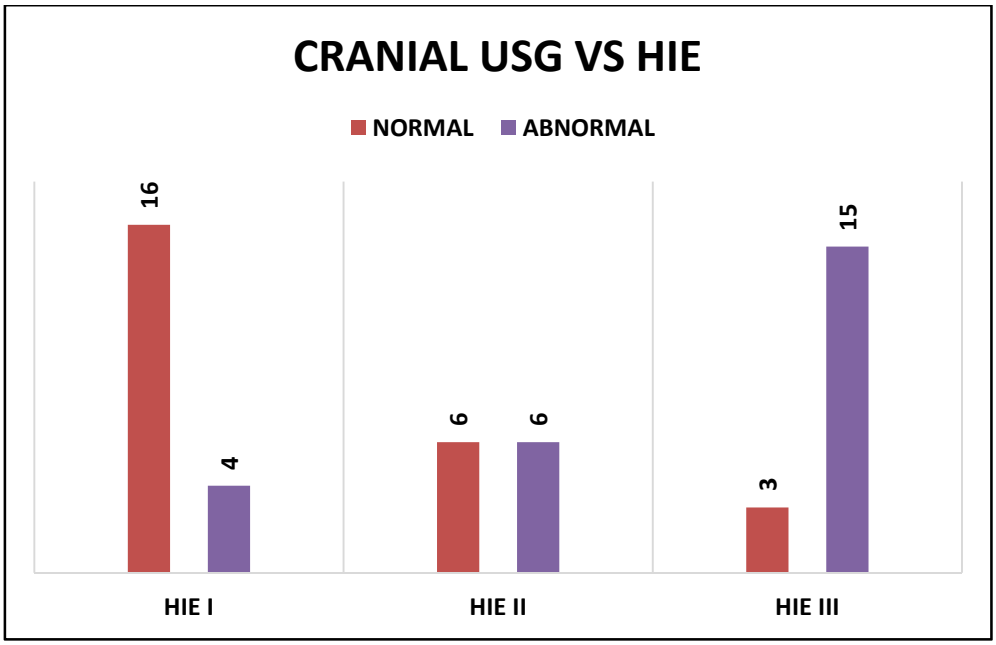


Table No: 21

ASSOCIATION BETWEEN ABNORMAL CRANIAL USG AND HIE (n=50).				
CRANIAL USG	HIE I	HIE II	HIE III	TOTAL(%)
NORMAL	16	6	3	25(50)
ABNORMAL	4	6	15	25(50)
TOTAL	20	121	18	50
KRUSKAL WALLIS TEST				
P VALUE - 0.005				

P VALUE was found to be .005, which shows significant statistical correlation between HIE severity and cranial ultrasound.

Table 22

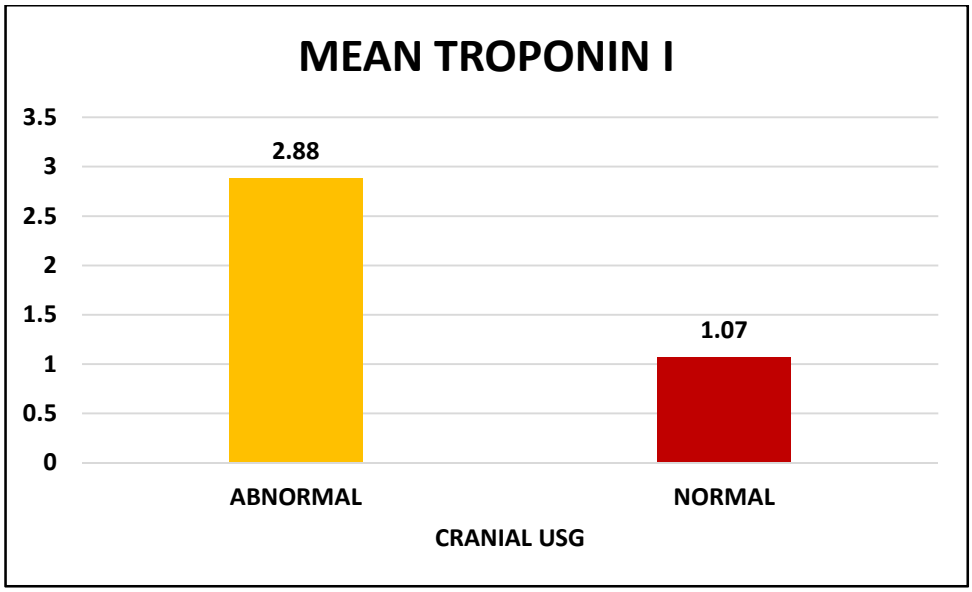
DISTRIBUTION BASED ON MEAN TROPOIN I LEVELS AND CRANIAL USG

	TROPONIN I LEVEL	
CRANIAL USG	MEAN	SD
ABNORMAL	2.88	1.5
NORMAL	1.07	1.13
UNPAIRED T TEST		
P VALUE - 0.040		

Cranial ultrasound and Troponin I LEVELS were compared which shows statistical significance of P VALUE-.040

Figure 24

MEAN TROPONIN I LEVELS AMONG ABNORMAL CRANIAL USG BABIES



The mean Troponin I levels was 2.88ng/ml among babies with abnormal cranial ultrasound. The mean Troponin I level was 1.07ng/ml among babies with normal cranial ultrasound.

Table 23

ASSOCIATION BETWEEN TROPONIN I LEVELS AND HIE (N=50)					
TROPONIN I LEVEL	HIE I	HIE II	HIE III	TOTAL	PERCENTAGE
INCREASED	1	7	16	24	48%
NORMAL	19	5	2	26	52%
TOTAL	20	12	18	50	
KRUSKAL WALLIS TEST					
P VALUE - 0.001					

While comparing troponin I levels with HIE severity, HIE III neonates had more elevated troponin I levels when compared to HIE I & II,P VALUE was statistically significant.

Figure 25

Association between Troponin I levels and HIE

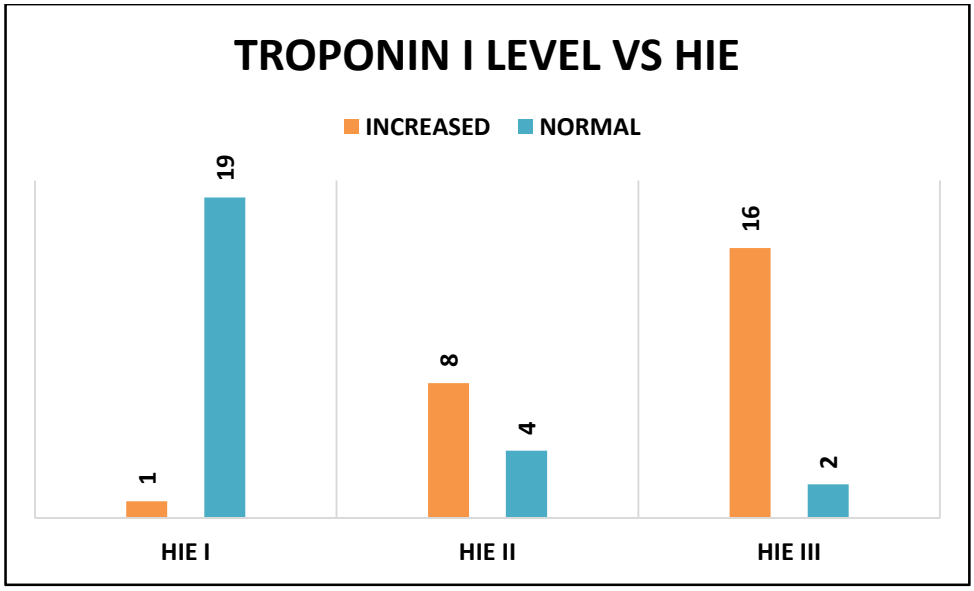


Figure 26

Distribution based on elevated Troponin I levels

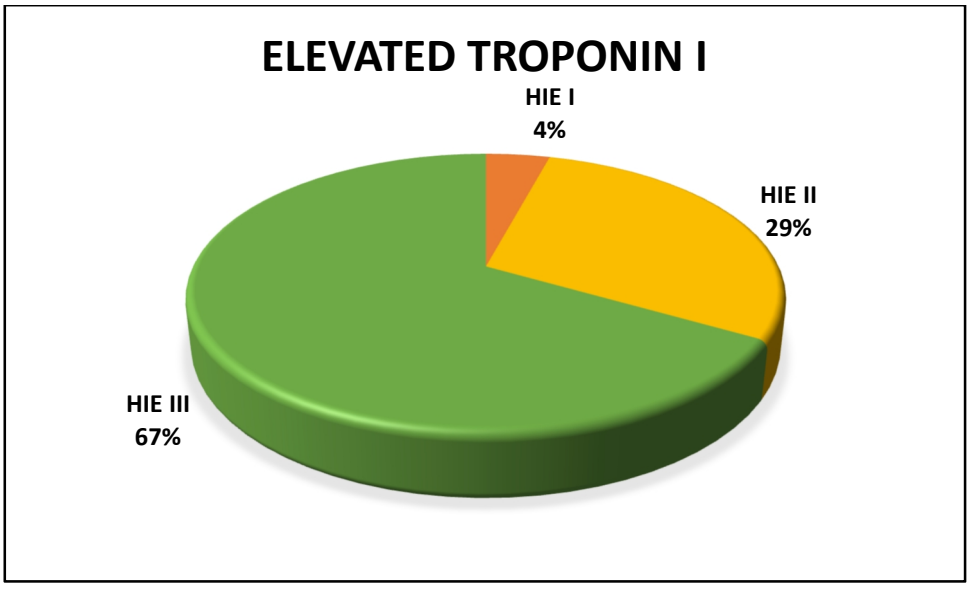


Table 24

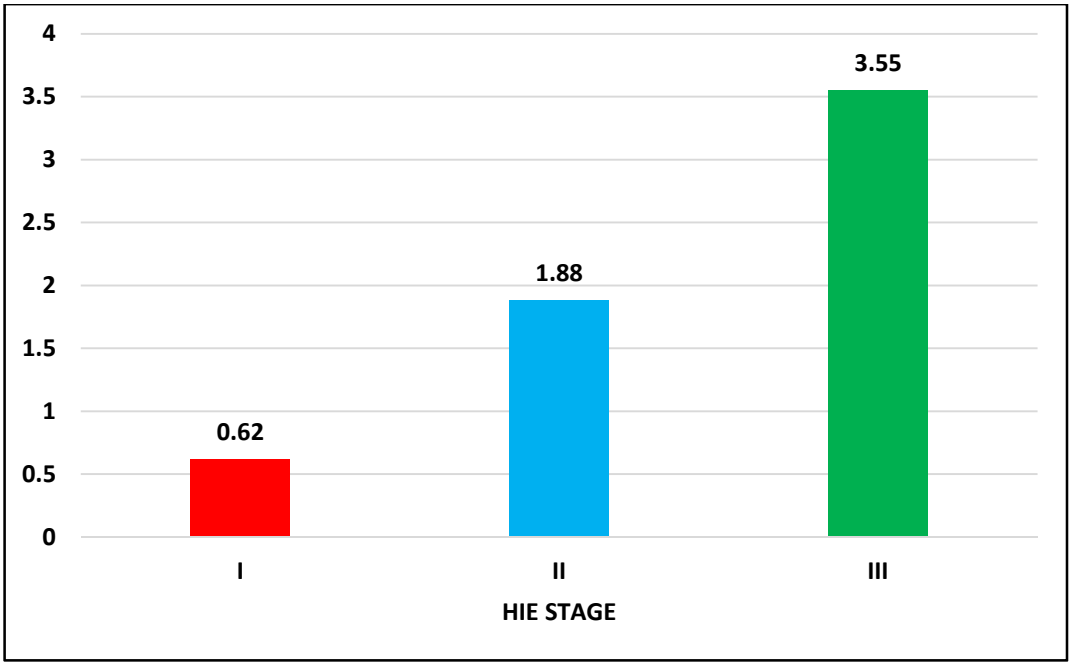
DISTRIBUTION BASED ON MEAN TROPONIN I LEVELS AND HIE

	TROPONIN I LEVEL	
HIE	MEAN	SD
I	0.62	0.56
II	1.88	1.25
III	3.55	1.12
ANOVA		
P VALUE - 0.001		

Among the HIE babies ,the mean Troponin I levels were found to be increased among HIE III which was higher when compared to HIE II babies and HIE I babies,with a statistically significant P VALUE.This confirms that HIE severity could be predicted earlier with Troponin I levels.

Figure 27

Mean Troponin I Levels among HIE



Bar diagram showing the mean Troponin I levels among HIE I, II and III. Mean Troponin I levels was 3.55ng/ml in HIE III which is more than HIE I and II.

Table 25

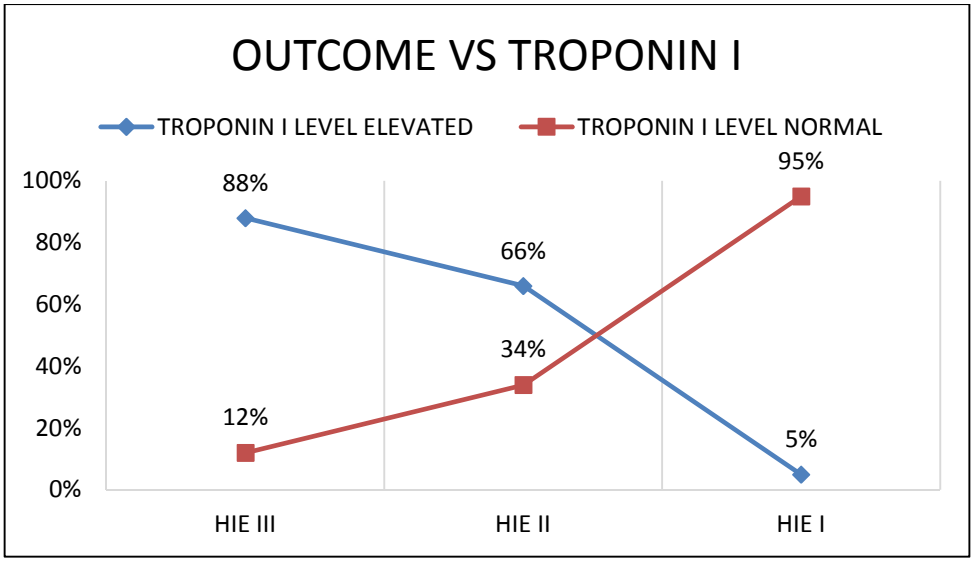
ASSOCIATION BETWEEN OUTCOME OF HIE AND TROPONIN I LEVELS

OUTCOME	TROPONIN I LEVEL	
	ELEVATED	NORMAL
HIE III	16	2
HIE II	7	5
HIE I	1	19
KRUSKAL WALLIS TEST		
P VALUE - 0.001		

The P VALUE was statistically significant when outcome of HIE was compared with troponin I levels

Figure 28

Association between Outcome of HIE and Troponin I levels



Among the HIE III babies Troponin I levels were elevated in 16 out of 18 babies, 7 out of 12 HIE II babies and 1 out of 19 HIE I babies. This showed that Troponin I levels were significantly high in HIE III babies with a significant P VALUE.

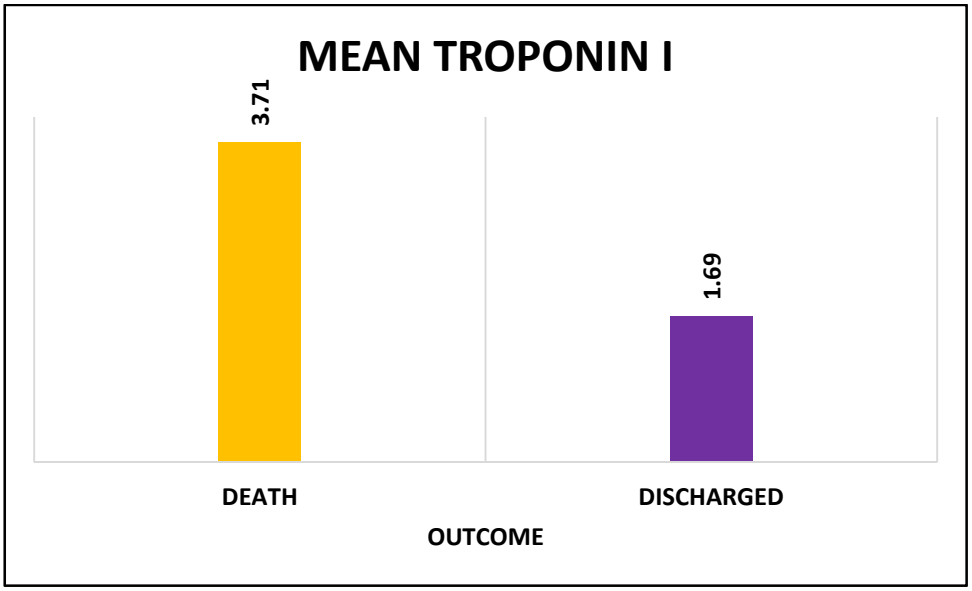
Table No :26

MEAN TROPONIN I LEVELS AMONG DEATH BABIES

	TROPONIN I LEVEL	
OUTCOME	MEAN	SD
DEATH	3.71	1.15
DISCHARGED	1.69	1.49
UNPAIRED T TEST		
P VALUE - 0.013		
SIGNIFICANT		

Figure 29

MEAN TROPONIN I LEVELS AMONG DEATH BABIES



The mean troponin I value of death neonates in HIE -3.71ng/ml.

The mean troponin I values of discharged neonates in HIE-1.69ng/ml.

DISCUSSION

Perinatal asphyxia accounts for the leading cause of neonatal death[35], various studies have been done previously to identify the risk factors predicting the morbidity and mortality in perinatal asphyxia. Hypoxic myocardial injury in perinatal asphyxia is one of the major causes of death, which could be identified by various cardiac markers like Troponin I and troponin T. There is a need for early identification of myocardial injury to achieve timely hemodynamic stability and some early prognostic indicator to determine the morbidity and mortality in HIE [36].

The aim of our study is to measure Troponin I within 6 hours of life, and to compare it with HIE severity and myocardial injury[37].Severity in HIE was determined by the presence of seizures, shock, ventilator requirement and cranial ultrasound . Myocardial injury was determined by taking ECG & ECHO at 24 and 48 hours of life, presence of shock and duration of inotropic support.

The study was conducted in Sick Neonatal Care Unit, paediatrics department Tirunelveli medical college during the period of march 2017 to february 2018.

Around 50 neonates with APGAR score of < 7 @ one minute of life as per WHO –NEONATAL PERINATAL DATA BASE were included in

the study. They were graded as HIE I (mild), II (moderate) and III (severe) based on SARNAT SARNAT STAGING [11] done at 24 hours of life. These babies were followed and their outcome in the form of morbidity and mortality were analysed.

Totally 50 neonates were studied. Among them 20(40%) progressed to HIE I,12(24%) to HIE II and18(36%) to HIE III.

In our study gravida, gestational age, mode of delivery, sex and birth weight did not show statistical significance when compared with severity of HIE and elevated Troponin I levels .This was comparable with the study done by Ahmed T Mahmoud Ayat shebl et al [29].

Among the 50 neonates studied, 26(52%) had seizures and 24(48%) of babies had no seizures. Among the 26 babies with seizures , 10/12 belong to HIE II and 16/18 belonged to HIE III. Seizures in HIE showed a highly significant correlation with a P VALUE – 0.001[29].

Among the 24 neonates with elevated Troponin I, 19 neonates had seizures and among 26 babies with normal troponin I only 7 had seizures, which shows troponin I levels and seizures was comparable with a significant P value of 0.002.This is in agreement with the study done byTurker et al who found that neurological disorders in a newborn is primarily due to cerebral hypoxia.

The ventilator requirement was compared with elevated Troponin I levels, Among the 24 neonates with elevated troponin I levels 18 out of 24 (75%) required ventilator support whereas among the 26 neonates with normal Troponin I only 7 out of 26 (26%) required ventilator support. As already known the ventilator requirement signifies the severity of HIE ,now it shows a positive correlation between elevated troponin I and ventilator requirement with a P VALUE of 0.006.

Presence of shock compared with serum Troponin I levels. Among the 24 neonates with elevated troponin I levels, 22 out of 24 (91%) developed shock, whereas among babies with normal Troponin I only 5 out of 26(19%) developed shock. This shows that elevated Troponin I levels had a significant influence on shock with a P VALUE of 0.001.

Among the 27 neonates with shock, the duration of inotropic support was compared with HIE severity and elevated Troponin I levels.6 out of 10 babies of HIE II with shock required inotropes for more than 48 hours and out of the 17 babies of HIE III with shock,14 out of 17 babies required inotropes for more than 48 hours with a P value of 0.035 which shows a significant statistical correlation. This is in agreement with shastri et al, who studied the cardiac troponin I levels with HIE and found that serum troponin I levels and duration of inotropic support were significantly greater with increasing severity of HIE[37]. . Early cTnI concentrations may

provide a useful proxy marker for the anticipated severity of myocardial dysfunction.

Renal parameters were compared with HIE severity and troponin I levels. Among the 50 neonates studies 28/50 (56%) had elevated renal parameters and 22/50 had normal renal parameters. Out of the 22 babies with elevated renal parameters,2/20 belonged to HIE I,8 /12 belonged to HIE II and 12/18 belong to HIE III. Elevated renal parameters showed a significant positive correlation with HIE severity with a p value of 0.004.This was comparable with the study done by Ahmed T Mahmoud et al[29].

Elevated renal parameters were compared with troponin I levels, 19/24 babies with elevated troponin I had abnormal renal parameters, whereas 4/26 babies with normal troponin I levels had abnormal renal parameters. This showed a significant correlation between abnormal renal parameters and troponin I levels with a P value of 0.001.Troponin I levels were significantly elevated in those with increased renal parameters thus predicts the severity of HIE.

Electrocardiogram taken at 24 and 48 hours of life was compared with elevated troponin I levels. Abnormal ECG was compared with HIE severity. Among the 50 neonates, 54% had normal ECG and 46 % had abnormal ECG. Among the 27(54%) with abnormal ECG, 15 were from

HIE III,9 from HIE II AND 3 from HIE I. Abnormal ECG and HIE severity showed significant positive correlation with a P VALUE – 0.03[38,26].

The distribution between the mean Troponin I levels and ECG was analysed, which showed the mean Troponin I levels in babies with abnormal ECG was found to be 3.1ng /ml, which was significantly higher with the mean Troponin I levels of 0.65ng/ml in babies with normal ECG, with a P VALUE of 0.001.

ECHOCARDIOGRAM with HIE severity was compared, which showed a statistically highly significant P VALUE of 0.001.The mean Troponin I levels (3.2ng/ml) in babies with abnormal ECHO was compared with the mean troponin I levels(0.64ng/ml) in babies with normal ECHO, which showed a significant correlation with a P VALUE of 0.001[26].

This concludes that mean troponin I levels in cases with cardiac dysfunction (as evidenced by ECG and ECHO abnormality) was found significantly higher in cases with severe asphyxia. This was in agreement with the study ECG changes in birth asphyxia and its correlation with cardiac troponin I done by Dr.Pankaj et al

Cranial ultrasound was compared with severity of HIE. Among the 50 asphyxiated babies ,15/18 from HIE III,6/12 from HIE II and 3/20 from HIE I had abnormal cranial ultrasound. As the severity increases the percentage of abnormal USG increases, which shows a significant positive correlation between severity of HIE and abnormal Cranial USG[29]. This was comparable with the study done by Ahmed T Mahmoud.

The mean troponin I levels in babies with abnormal cranial USG was 2.88ng/ml which was significantly higher than the mean troponin I levels(1.07ng/ml) in babies with normal cranial USG ,with a significant P VALUE of 0.005.This concluded that troponin I levels correlates well with HIE severity as evidenced by abnormal cranial ultrasound.

CARDIAC TROPONIN I

Cardiac troponin I levels were compared with HIE severity[39].HIE III neonates(16/18) had more elevated troponin I levels when compared with HIE II(7/12) and HIE I(1/20).P VALUE was statisticaly highly significant .The mean troponin I levels in HIE III was found to be 3.55±1.12,which was higher when compared to the mean troponin I levels in HIE II (1.88±1.25) and HIE I (0.62±0.56)[40].The P VALUE of 0.001 showed a significant positive correlation between HIE severity and Troponin I levels[41].This was in agreement with the study done by Roopa B et al and Montaldo et al.

The outcome in HIE was compared with troponin I levels[42]. Among the 24 babies with elevated troponin I , 10/11 HIE III babies had elevated troponin I , 7/12 HIE II babies had elevated troponin I , only 1/20 HIE I babies had elevated troponin I levels. The P VALUE was statisticaly highly significant – 0.001, when the outcome of HIE was compared with troponin I levels. The results were comparable with the study done by Alexandra M.simovac.

Finally , mean troponin I levels in death babies were found to be 3.71ng/ml and the mean troponin I levels in discharged babies was found to be 1.69ng/ml. This showed that asphyxiated babies with a P VALUE more than 3.71ng/ml , the mortality is very high. Asphyxiated babies with elevated Troponin I levels is considered to be a predictor / risk factor for mortality.

CONCLUSION

1) Gravida, gestational age, mode of delivery, sex distribution and birth weight did not have a impact on HIE severity and myocardial dysfunction.
2) Measuring troponin I levels within 6 hours of life showed statistical significant abnormalities in ECG, ECHO, presence of shock and need for inotropic support. Early cTnI concentrations may provide a useful proxy marker for the anticipated severity of myocardial dysfunction, which would help the NICU team to achieve timely hemodynamic stability thereby influencing the outcome of asphyxiated babies.
3) Elevated Troponin I levels had a statisticaly significant impact on the severity determining factors of HIE like seizures, ventilator requirement and abnormalities in cranial ultrasound . Hence Cardiac troponin I is considered to be a very sensitive and early biochemical marker of ischemic myocardial injury that helps in early prediction of mortality in perinatal asphyxia patients.
4) Cardiac Troponin I levels of 1.7 ng/ml has been observed as a cut off value between mild and moderate to Severely asphyxiated neonates.

5) 3.55 ng/ml has been observed as a cut off value for severely Asphyxiated neonates.
6) Cardiac Troponin I levels of 3.71 ng/ml has been associated with a high mortality in severely Asphyxiated neonates.

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SARNAT AND SARNAT STAGES OF HYPOXIC ISCHEMIC ENCEPHALOPATHY

Stage	Stage 1 (Mild)	Stage 2 (Moderate)	Stage 3 (Severe)
Level of consciousness	Hyperalert; irritable	Lethargic or obtunded	Stuporous, comatose
Neuromuscular control:	Uninhibited, overreactive	Diminished spontaneous movement	Diminished or absent spontaneous movement
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive, disinhibited	Decreased or absent
Segmental myoclonus	Present or absent	Present	Absent
Complex reflexes:	Normal	Suppressed	Absent
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function:	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Midposition, often unequal; poor light reflex
Respirations	Spontaneous	Spontaneous; occasional apnea	Periodic; apnea
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable

Gastrointestinal motility	Normal or decreased	Increased, diarrhea	Variable
Seizures	None	Common focal or multifocal (6-24 hours of age)	Uncommon (excluding decerebration)
Electroencephalographic findings	Normal (awake)	Early: generalized low voltage, slowing (continuous delta and theta)	Early: periodic pattern with isopotential phases
		Later: periodic pattern (awake); seizures focal or multifocal; 1.0-1.5 Hz spike and wave	Later: totally isopotential
Duration of symptoms	<24 hours	2-14 days	Hours to weeks
Outcome	About 100% normal	80% normal; abnormal if symptoms more than 5-7 days	About 50% die; remainder with severe sequelae

S.No.	Name	Gravida	Mode of Delivery	Sex	Gestational Age	Birth Weight	Seizures	Ventilator Support	Shock	Duration of Ionotropic Suport	Renal Parameters	Troponin I mg/ml	ECG	ECHO	Cranial USG	HIE	Outcome
1	B/o Mupidathi	P	LSCS	M	39	3.2	Yes	Yes	Yes	>24	↑	4.3	ABN	ABN	ABN	III	Death
2	B/o Esakkiammal	P	LN	M	39	3.3	No	No	No	<24	N	0.5	ABN	ABN	N	I	Discharged
3	B/o Suganya	M	LN	F	39	3.15	Yes	Yes	Yes	>24	↑	3.2	ABN	ABN	ABN	II	Discharged
4	B/o Iswarya	M	LN	M	38.4	3	Yes	No	Yes	>24	↑	4	ABN	ABN	AB	III	Death
5	B/o Bavithra	P	LSCS	M	38	2.8	No	No	No	-	N	0.5	N	N	N	II	Discharged
6	B/o Muthulakshmi	P	LN	M	40	3.1	No	Yes	No	>24	↑	4.2	ABN	ABN	AB	III	Death
7	B/o Priyadharshini	P	LSCS	M	39	3.25	Yes	Yes	Yes	>24	↑	2.8	ABN	ABN	ABN	II	Discharged
8	B/o Santhanamari	P	LN	F	39	3.1	No	No	No	-	N	0.45	N	N	N	I	Discharged
9	B/o Mariselvi	M	LSCS	M	39.2	2.8	Yes	Yes	Yes	>24	↑	1.1	ABN	ABN	AB	III	Death
10	B/o Muthusoundarya	P	LN	M	38.4	3.125	No	No	No	-	N	0.52	N	N	N	I	Discharged
11	B/o Mariyal	P	LN	M	38.6	2.5	Yes	Yes	Yes	-	↑	1.2	N	N	N	III	Discharged
12	B/o Sudha	P	LN	F	39	2.56	No	No	No	-	N	0.51	N	N	N	I	Discharged
13	B/o Kanmani	M	LN	F	38	3.2	Yes	Yes	Yes	>24	↑	4	ABN	ABN	ABN	III	Death
14	B/o Jothilakshmi	P	LN	F	38.4	2.75	No	No	No	-	N	0.49	N	N	N	II	Discharged
15	B/o Maria jenita	P	LSCS	F	38	3.05	Yes	Yes	Yes	>24	N	3.9	ABN	ABN	ABN	III	Discharged
16	B/o Amuthavalli	P	LN	M	40	3.25	No	No	Yes	<24	↑	0.52	ABN	ABN	ABN	I	Discharged
17	B/o Jeyanthi	P	LSCS	M	40	3.12	Yes	Yes	Yes	<24	↑	2.5	ABN	ABN	N	II	Discharged
18	B/o Thamilselvi	M	LN	M	40	2.7	No	Yes	Yes	<24	↑	1.1	N	N	ABN	III	Discharged
19	B/o Mumthaj	P	LSCS	F	39.2	3.41	Yes	Yes	No	-	N	0.5	N	N	ABN	I	Discharged
20	B/o Lakshmi	M	LN	F	38.3	3.42	Yes	Yes	Yes	>24	N	3.2	ABN	ABN	N	II	Discharged
21	B/o Karpagavalli	P	LSCS	F	39	3.12	Yes	Yes	Yes	>24	↑	4.2	ABN	ABN	ABN	III	Discharged
22	B/o Kala	P	LN	M	38	3.4	No	No	No	-	N	0.5	N	N	ABN	I	Discharged
23	B/o Kalaiselvi	P	LSCS	M	38.6	3.5	Yes	Yes	No	-	N	0.49	ABN	N	N	II	Discharged
24	B/o Barani	P	LN	M	39	3.1	Yes	Yes	Yes	>24	↑	3.9	ABN	ABN	N	III	Discharged
25	B/o Chitra	P	LN	F	38.2	3.1	No	No	No	-	N	0.44	N	N	N	I	Discharged
26	B/o Divya	P	LN	F	37	3.3	Yes	Yes	Yes	>24	↑	4.1	ABN	ABN	ABN	III	Death
27	B/o Laltha	P	LN	F	37.5	2.6	No	No	No	-	N	0.7	N	N	ABN	II	Discharged
28	B/o Ilavarasi	M	LSCS	F	37.2	3	Yes	Yes	Yes	>24	N	4	ABN	ABN	ABN	III	Discharged
29	B/o Fathima	P	LN	M	40	3.29	No	No	Yes	<24	↑	1.8	ABN	ABN	N	I	Discharged
30	B/o Govindammal	M	LSCS	F	37.2	3.125	Yes	Yes	Yes	<24	↑	2	ABN	ABN	ABN	II	Discharged
31	B/o Jenneth	P4	LN	F	37.4	2.8	Yes	Yes	No	-	N	3.6	N	N	N	III	Discharged
32	B/o Jancy	P	LSCS	M	39	3.19	Yes	Yes	No	-	N	0.39	N	N	ABN	I	Discharged
33	B/o Kavitha	P	LSCS	M	37	3.15	No	No	No	-	N	0.35	N	N	N	I	Discharged
34	B/o Lavanya	M	LSCS	F	37	3.2	No	Yes	Yes	>24	↑	4.3	ABN	ABN	ABN	III	Death
35	B.o Murugammal	M	LSCS	M	37.4	2.2	No	No	No	-	N	0.4	N	N	N	I	Discharged
36	B/o Nithya	P	LN	M	37.2	3.41	Yes	Yes	Yes	>24	↑	3.3	ABN	ABN	ABN	II	Discharged
37	B.o Punitha	P	LN	M	37	3.1	Yes	Yes	Yes	>24	↑	4	ABN	ABN	ABN	III	Discharged
38	B/o Priya	M	LSCS	F	39	2.75	No	No	No	-	N	0.38	N	N	N	I	Discharged
39	B/o Renuka	M	LSCS	M	40	3.125	No	No	No	-	N	0.47	N	N	N	I	Discharged
40	B/o Maheswari	P	LN	M	37.2	2.81	Yes	Yes	Yes	<24	N	4.2	ABN	ABN	ABN	III	Discharged
41	B/o Vennila	M	LSCS	F	37	2.6	No	No	No	-	N	0.5	N	N	N	I	Discharged

S.No.	Name	Gravida	Mode of Delivery	Sex	Gestational Age	Birth Weight	Seizures	Ventilator Support	Shock	Duration of Ionotropic Suport	Renal Parameters	Troponin I mg/ml	ECG	ECHO	Cranial USG	HIE	Outcome
42	B/o Uma	P	LN	M	37.4	2.8	Yes	No	Yes	>24	↑	2.6	ABN	ABN	N	I	Discharged
43	B/o Vasuki	M	LSCS	M	37.2	2.75	No	No	No	-	N	0.53	N	N	N	I	Discharged
44	B/o Revathi	P	LSCS	M	37	3.1	No	No	Yes	-	N	3.8	ABN	ABN	ABN	III	Discharged
45	B/o Alagumari	M	LSCS	F	37	2.52	No	No	No	-	N	0.5	N	N	N	I	Discharged
46	B/o Aarthi	M	LSCS	F	37.4	2.6	No	No	No	-	N	0.2	N	N	N	I	Discharged
47	B/o Sathyapriya	P	LSCS	F	37.5	3.25	Yes	No	Yes	>24	↑	4	ABN	ABN	ABN	III	Discharged
48	B/o Sandhya	M	LSCS	F	39	2.5	No	No	No	-	N	0.36	N	N	N	I	Discharged
49	B/o Seetha	P	LN	M	37	3.26	No	No	Yes	>24	↑	3	ABN	ABN	ABN	II	Discharged
50	B/o Deepalakshmi	M	LSCS	F	36	2.6	No	No	-	-	N	0.4	N	N	N	I	Discharged